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UNIVERSITY OF ALBERTA

OUTCOME IN RHEUMATOID ARTHRITIS
A 1985 INCEPTION COHORT STUDY

BY

MARIA E SUAREZ-ALMAZOR ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial
fulfillment of the requirements for the degree of Doctor of Philosophy
in
Medicine (Epidemiology)

DEPARTMENT OF MEDICINE

Edmonton, Alberta
SPRING 1993

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ISBN 0-315-81990-1

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The undersigned certify that they have read, and recommended to the Faculty of Graduate Studies and Research for acceptance a thesis entitled 'Outcome in Rheumatoid Arthritis. A 1985 Inception Cohort Study' submitted by Maria E Suarez-Almazor for the degree of Doctor of Philosophy in Medical Sciences.

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Dated .... Feb 10, 93

To Eduardo, Ed, Sofia
and Sebastian

ABSTRACT

The purpose of this study was to examine the outcome of rheumatoid arthritis (RA) in a 1985 inception cohort, historically established. All patients in Edmonton with RA confirmed by a rheumatologist and with an onset of disease in 1985 were eligible for the cohort. Of these, 128 (75%) participated in the study. Approximately 40% of them had a remittive course. As expected, patients with a chronic course had more severe outcomes.

Thirty percent of the patients had normal functional status. X-rays were normal in a third. Most patients had received remittive therapy within the first 2 years; 85% had received at least one drug. In the 70 patients who had received parenteral gold, duration of therapy was significanlty associated with better outcome and lower radiological scores.

Bivariate and multivariate analyses including multiple and logistic regressions, and LISREL showed that the associations varied according to the measure employed. The major determinants of disease activity were rheumatoid nodules, rheumatoid factor (RF) and female gender. Radiological damage was associated with disease activity. RF was associated with radiological damage only indirectly through disease activity. Functional status was strongly associated with disease activity and income. No significant associations were observed between function and RF or function and radiological scores.

The multivariate analyses suggested that two different dimensions defined outcome and clinical status, the first one related to articular damage and the second to function. Disease activity was significantly associated with both. Sociological variables, especially income, were associated with disability, with patients in the lower strata having decreased function.

This study was conducted in an inception cohort as opposed to most previously published reports based on prevalent cases. This reduces the probability of bias and may explain the relatively better prognosis observed.

Rheumatoid arthritis remains a complex disease, with multiple outcome dimensions. Further research is necessary to discriminate between biological and social impacts.

ACKNOWLEDGEMENTS

I thank my co-supervisors Dr Anthony Russell and Dr Colin Soskolne for their guidance and support throughout this project. I am also grateful to the other members of my supervisory committee, Dr Duncan Saunders and Dr Leslie Hayduk, for their suggestions and assistance in the design and analysis of the study.

Dr John Esdaile, Dr Stephen Newman and Dr Paul Davis, reviewed the dissertation and provided valuable comments and recommendations.

Special thanks go to all the rheumatologists in Edmonton who gave me unrestricted access to their patients and medical charts: this study would not have been possible without the help of Dr Stephen Aaron, Dr Peter Chiu, Dr Paul Davis, Dr Avril Fitzgerald, Dr Sharon LeClercq, Dr John Percy, Dr Anthony Russell, Dr Savitri Senaratne and Dr Alex Yan.

Dr Walter Maksymowych and the staff at the Rheumatic Disease Unit laboratory performed the HLA DR4 typing and antinuclear antibodies tests, and deserve acknowledgement for their efforts.

Finally, very special thanks go to all the patients with rheumatoid arthritis that participated in this study. Clinical investigation would not be possible without the altruistic and generous help of patients, who volunteer for research even though the benefits of specific projects may not be achieved in their lifetimes.

TABLE OF CONTENTS

PAGE

CHAPTER 1. INTRODUCTION

GENERAL DESCRIPTION OF RHEUMATOID ARTHRITIS 1

1. Epidemiology of rheumatoid arthritis 2
2. General characteristics 3
    - 2.1 Clinical features 3
    - 2.2 Radiological features 7
    - 2.3 Laboratory features 8
3. Treatment of rheumatoid arthritis 10
    - 3.1 Patient education 10
    - 3.2 Physical therapy and rehabilitation 11
    - 3.3 Non-steroidal antiinflammatory drugs 12
    - 3.4 Steroids 13
    - 3.5 Second-line drugs 13
    - 3.6 Injections of joints and soft tissues 19
    - 3.7 Surgery 19

CHAPTER 2. REVIEW OF THE LITERATURE

OUTCOME IN RHEUMATOID ARTHRITIS 21

1. Outcome measures 23
    - 1.1 Disease activity 23
    - 1.2 Radiological damage 26
    - 1.3 Functional status 27
    - 1.4 Mortality 29

1.5 Other 30

2. Overall prognosis: review of long-term studies 30

3. Prognostic factors 33

3.1 Age 33

3.2 Gender 34

3.3 Type of onset 34

3.4 Clinical features 35

3.5 Rheumatoid factor 35

3.6 Antinuclear antibodies 35

3.7 HLA associations 36

3.8 Therapy 37

3.9 Socioeconomic status 38

3.10 Psychosocial factors 39

CHAPTER 3. RATIONALE AND OBJECTIVES OF THE STUDY 40

1. Limitations of previous studies 41

2. Objectives and hypotheses 45

2.1 Descriptive objectives 46

2.2 Analytic objectives 46

2.3 Hypotheses 47

3. Relevance of this study 48

CHAPTER 4. PATIENTS AND METHODS 49

1. Design of the study 50

2. Selection of the study cohort 50

2.1 Initial selection of potential cases 51

2.2 Review of medical charts 52

2.3 Definite inclusion in cohort 53

3. Temporal sequence of the study 54

4. Validation of the inception cohort 55

5. Procedures and instruments 56

5.1 Extraction of medical chart information 56

5.2 Personal interview 57

5.3 Physical examination 57

5.4 Self-response questionnaire 59

5.5 Radiographs of the hand 60

5.6 Laboratory tests 62

5.7 HLA-DR4 typing 63

6. Study variables 63

7. Clinical status and outcome measures 63

8. Statistical methods 65

8.1 Bivariate analysis 65

8.2 Multivariate analysis 66

9. Statistical power 69

10. Ethics approval 70

CHAPTER 5. RESULTS 1

SELECTION OF THE 1985 INCEPTION COHORT 71

1. Initial selection of the 1985 cohort 72

2. Final selection of the 1985 cohort 73

3. Comparisons of participants with non-participants 75

4. Results of the physician survey 75

CHAPTER 6. RESULTS 2

CHARACTERISTICS OF THE 1985 COHORT. OVERALL OUTCOME 82

1. General characteristics of the cohort 83
    - 1.1 Demographic characteristics 83
    - 1.2 Diagnosis of RA according to the ACR criteria 83
    - 1.3 Clinical characteristics 84
    - 1.4 Disease activity at time of assessment 87
    - 1.5 Rheumatoid factors and antinuclear antibodies 88
    - 1.6 Radiological changes 89
    - 1.7 Functional status 89
    - 1.8 Remission 90
2. Course of disease and associations with other disease characteristics 91
3. Bivariate analysis: associations of outcome measures 92
    - 3.1 Demographic characteristics 92
    - 3.2 Type of onset 94
    - 3.3 Rheumatoid factor 94
    - 3.4 HLA DR4 94
    - 3.5 Nodules 95
    - 3.6 Sociological variables 95
4. Associations among outcome measurements 96

CHAPTER 7. RESULTS 3

THERAPY 113

1. Current use of second-line drugs 114

2. Characteristics of the use of second-line drugs during the course of the disease 114
    - 2.1 Second-line drugs prescribed 114
    - 2.2 Combination therapy 116
    - 2.3 Selection of first second-line drug 117
    - 2.4 Choice of second-line drugs during the course of the disease 117
    - 2.5 Physicians' variations in use of second-line drugs 118
    - 2.6 Duration of therapy 119
    - 2.7 Discontinuation of second-line therapies 120
    - 2.8 Efficacy of second-line drugs 121

3. Use of corticosteroids 122

4. Utilization of some health services 123
    - 4.1 Consults to rheumatologists 123
    - 4.2 Other 124

5. Surgery 125

6. Alternative medicine 125

CHAPTER 8. RESULTS 4

MULTIVARIATE ANALYSIS. MULTIPLE LINEAR REGRESSION 139

1. Disease activity 140

2. Articular damage 143

3. Functional status 143

4. Other models 144

CHAPTER 9. RESULTS 5

MULTIVARIATE ANALYSIS. LOGISTIC REGRESSION 149

1. Disease activity 150
2. Articular damage 153
3. Functional status 154

CHAPTER 10. RESULTS 6

LISREL MODELS 164

1. Model 1 166
2. Model 2 169
3. Model 3 170

CHAPTER 11. DISCUSSION AND CONCLUSIONS 178

1. Discussion 179
    1.1 Overall prognosis 180
    1.2 Therapy 184
    1.3 Determinants of clinical status and outcome 188
2. Conclusions 194
3. Recommendations for future research 196

REFERENCES 198

APPENDICES

Appendix 1: Letter to patient 218
Appendix 2: ARA criteria for RA diagnosis 220
Appendix 3: Physician survey form 222
Appendix 4: Medical chart review form 225

Appendix 5: Personal interview form 230

Appendix 6: Self-response questionnaire 238

Appendix 7: Variable codebook 243

Appendix 8: LISREL computer output - Model 1 263

Appendix 9: LISREL computer output - Model 3 272

LIST OF TABLES

PAGE

TABLE 5.1 Distribution of patients with RA according to onset, after review of the medical charts 77

TABLE 5.2 Patient status in relation to the inception cohort according to source of information 78

TABLE 5.3 Patient status in relation to the inception cohort according to onset status in medical chart 79

TABLE 5.4 Characteristics of patients in the cohort vs non-participants 80

TABLE 5.5 Results of the physicians survey. Percentage of patients seen by rheumatologists 81

TABLE 6.1 Demographic characteristics of the 1985 inception cohort 97

TABLE 6.2 American Rheumatism Association criteria for the diagnosis of RA in the 1985 inception cohort 98

TABLE 6.3 Course of RA according to type of onset 99

TABLE 6.4 Demographic characteristics according to course of RA 100

TABLE 6.5 Joint indices, rheumatoid nodules and hand deformities according to course of RA 101

TABLE 6.6 Other outcome measurements according to course of RA 102

TABLE 6.7 Rheumatoid factors, HLA DR4 and ANA according to course of RA 103

TABLE 6.8 Clinical characteristics and indices according to gender 104

TABLE 6.9 Clinical characteristics and joint counts according to type of onset 105

TABLE 6.10	Outcome measures, ANA, RF and HLA DR4 according to type of onset	106
TABLE 6.11	Clinical characteristics and indices according to RF status	107
TABLE 6.12	Clinical characteristics and indices according to HLA DR4 status	108
TABLE 6.13	Clinical characteristics and indices according to the presence of rheumatoid nodules	109
TABLE 6.14	Clinical characteristics and indices according to education and economic status	110
TABLE 6.15	Demographic and clinical characteristics according to marital status	111
TABLE 6.16	Correlation matrix for outcome measures	112
TABLE 7.1	Current use of second-line drugs	127
TABLE 7.2	Use of second-line drugs during the course of RA	128
TABLE 7.3	Choice of different second-line drugs during the course of RA	129
TABLE 7.4	Prescription of second-line drugs by different rheumatologists	130
TABLE 7.5	Prescription of first second-line drugs by different rheumatologists	131
TABLE 7.6	Discontinuation of second-line drugs	132
TABLE 7.7	Survival time analysis for various second-line drugs (6 to 24 months)	133
TABLE 7.8	Survival time analysis for various second-line drugs (30 to 48 months)	134
TABLE 7.9	Frequency of side effects for the different drugs	135

TABLE 7.10	Correlations between duration of therapy with the different drugs and outcome measures	136
TABLE 7.11	Duration of therapy with GSTM and outcome measures in 70 patients treated with GSTM	137
TABLE 8.1	Linear multiple regression model (stepwise method) with the number of swollen joints as dependent variable (model 1)	145
TABLE 8.2	Linear multiple regression model with the number of swollen joints as dependent variable (model 2)	146
TABLE 8.3	Linear multiple regression model (stepwise method) with the radiological score as dependent variable	147
TABLE 8.4	Linear multiple regression model (stepwise method) with the MHAQ-ADL score as dependent variable	148
TABLE 9.1	Categorization of patients according to the number of swollen joints (low, high) and predictor variables	156
TABLE 9.2	Logistic regression model using the number of swollen joints (low vs high) as outcome variable	157
TABLE 9.3	Categorization of patients according to the radiological score (low, high) and predictor variables	158
TABLE 9.4	Logistic regression model using the radiological score (low vs high) as the outcome variable	159
TABLE 9.5	Selected logistic regression models using the radiological score (low vs high) as the outcome variable	160
TABLE 9.6	Categorization of patients according to the MHAQ-ADL score (low, high) and predictor variables	161

TABLE 9.7 Logistic regression model using the MHAQ-ADL score (low vs high) as the outcome variable 162

TABLE 9.8 Selected logistic regression models using the MHAQ-ADL score (low vs high) as the outcome variable 163

LIST OF FIGURES

		PAGE
FIGURE 1.1	Treatment pyramid for rheumatoid arthritis	20
FIGURE 7.1	Year of initiation of second-line therapy	138
FIGURE 10.1	LISREL model 1	174
FIGURE 10.2	LISREL model 1, results	175
FIGURE 10.3	LISREL model 2	176
FIGURE 10.4	LISREL model 3, results	177

ABBREVIATIONS

ACR	American College of Rheumatology
ADL	Activities of daily living
ANA	Antinuclear antibodies
ARA	American Rheumatism Association
DIP	Distal interphalangeal
DMARDS	Disease-modifying antirheumatic drugs
ENA	Extractable nuclear antigen
ESR	Erythrocyte sedimentation rate
GSTM	Sodium aurothiomalate
HLA	Human leukocyte antigens
LISREL	Linear structural relations
MCP	Metacarpophalangeal
MHAQ	Modified health assessment questionnaire
MTP	Metatarsophalangeal
NSAIDS	Non-steroidal antiinflammatory drugs
OR	Odds ratio
PCR	Polymerase chain reaction
PIP	Proximal interphalangeal
RA	Rheumatoid arthritis
RF	Rheumatoid factor
ROM	Range of motion
VAS	Visual analogue scale

CHAPTER 1

INTRODUCTION

GENERAL DESCRIPTION OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disorder of unknown etiology. It is characterized by a chronic polyarthritis affecting primarily the diarthrodial joints and related periarticular tissues [1]. Although there is considerable knowledge in relation to the pathogenesis of RA and the events leading to inflammation and joint destruction, the ultimate causative factors are still unknown. The available evidence suggests a multifactorial etiology with a genetically susceptible host being exposed to one or more putative agents *(102, 185, 279, 298)*.

1. EPIDEMIOLOGY OF RA

(12, 53, 61, 114, 121, 122, 132, 138, 140, 141, 150, 162, 172, 282)

The prevalence of RA varies in different series from 0.3 to 1.5% of the population. This variability may be due in part to different methods of collecting information. Annual incidence rates vary among studies. A 1980 study from the Mayo Clinic estimated the annual incidence of RA in Rochester, Minnesota, for the period 1970-1974, as 34.2 per 100,000 *(150)*. Recent studies have reported somewhat lower rates *(1252, 253, 274)*. The cause for this variation is unknown and differences in study methodologies probably play a role. Although controversial, it also has been suggested that the rates may have truly decreased because of the protective effect from contraceptive hormones *(74, 110, 270, 280)*. In general, population studies basing the diagnosis of RA on information obtained from self-reported surveys (telephone surveys, mailed questionnaires) appear to overestimate both the incidence and prevalence of the disease *(149, 171, 180)*.

---

[1] Because of the general nature of this review, references in this chapter are grouped and included for each major topic under the heading of the related section. Particular references to specific topics are provided throughout the chapter as required.

RA has a worldwide distribution and can occur in any ethnic group. Variations among different populations are small. Studies in North American aboriginals show somewhat increased rates *(19,36)*. A prevalence of 5.3% was reported for a band of Chippewa indians. A study in Yakima Indian women found a frequency of RA of 3.4% compared to 1.4% in the general population. Rural African blacks and Orientals appear to have a slight decrease in the prevalence of RA when compared to white populations *(17, 18, 129, 290)*.

RA is more common in women than men. The female:male ratio is 2-3:1. The disease can occur at any age. Several series have reported increasing incidence with age, with a peak around 50 years. A bimodal distribution also has been described with peaks in the 3rd and 5th decades *(162)*.

2. GENERAL CHARACTERISTICS

2.1. CLINICAL FEATURES

(12, 16, 32, 83, 84, 132, 162, 208)

A. Onset

Rheumatoid arthritis most frequently starts as an insidious symmetric polyarthritis, often with non-specific systemic symtoms such as malaise, fatigue, and on occasion, low-grade fever. Patients have pain and swelling usually in the hands, and very characteristically, marked morning stiffness that can last several hours. Occasionally, some individuals may present with mono or oligoarthritis that can persist for months, delaying the diagnosis. In some cases, the onset is acute, and patients develop a florid polyarthritis within a few days. Some individuals develop a syndrome named palindromic arthritis *(218)*. These patients complain of acute arthritis of one or more joints with pain and erythema, lasting for hours or days and subsiding spontaneously. Typically, patients remain asymptomatic between attacks. Approximately 30 to 50% of the patients with palindromic rheumatism will eventually develop RA. At that point, attacks become more frequent and the swelling does not subside completely between attacks.

B. Articular involvement

Once RA is established, the most characteristic picture is that of a symmetric polyarthritis affecting primarily the peripheral diarthrodial joints. Patients complain of joint pain, swelling and stiffness, with morning stiffness being a prominent feature when the disease is active. Over the years, as the disease progresses, muscular atrophy and structural damage may occur often leading to loss in the normal range of motion of the different joints and functional impairment. Secondary deformities can also occur at this point.

Hands and wrists: symmetric involvement of the small joints of the hands is the most prominent feature in RA, and is a major determinant in the functional outcome of patients. Metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints are the most frequent joints involved. Distal interphalangeal (DIP) joints are usually spared. Synovitis of the wrists is a common feature, frequently associated with carpal tunnel syndrome. Other related structures such as flexor and extensor tendons can also be involved. As the disease progresses structural damage and deformities may occur, and patients may lose essential functional capabilities related to the activities of daily life (ADL). Ulnar deviation and volar subluxation occur at the MCP level. "Swan neck" deformities of the fingers are secondary to hyperextension of the PIP and flexion of the

DIP joints, and affect grasp functions. "Boutonnière" deformities are related to flexion of the PIP and extension of the DIP.

Elbows and shoulders: elbows and shoulders can also be affected in RA, usually in patients with moderate to severe disease and widespread polyarthritis.

Feet: Foot involvement is very common with synovitis of the metatarsophalangeal (MTP) joints causing pain in the transverse arch. As the disease progresses, subluxation of the MTP heads, hallux valgus and claw deformities of the toes become common features.

Knees: Synovitis of the knees is common, with pain and swelling. Flexion deformities or ligament damage with joint instability can occur with persistent arthritis.

Cervical spine: The cervical spine is frequently involved in those patients with longstanding, progressive disease. A particular feature is the occurrence of atlanto-axial subluxation as a consequence of chronic involvement of the C1-C2 articulation, the odontoid process and the transverse ligament.

Other joints - Virtually any joint can be affected in RA. Nevertheless, the thoracic and lumbar spine are almost invariably spared. The ankles and the hips can be involved but not as often as the knees or the upper extremity joints.

C. Extraarticular involvement

Although RA is characterized mainly by a chronic polyarthritis, systemic manifestations are not unusual. Extraarticular involvement is crucial however, because unlike articular disease, it can lead directly to severe morbidity and death.

Non-specific systemic features - fatigue, anorexia, fever, malaise are common characteristics of RA, particularly at onset or during periods of increased disease activity. Lymphadenopathy and chronic anemia are also common at these times.

Rheumatoid nodules - Rheumatoid nodules occur in 20 to 30% of patients with RA. They are almost invariably associated with the presence of rheumatoid factors in serum, and often accompany other systemic manifestations. Rheumatoid nodules are typically found in the subcutaneous tissue of extensor surfaces but can also invade tendons, periosteum and bursae. Occcasionally they can be found in central organs such as the heart and lungs.

Vasculitis - clinical vasculitis usually occurs in patients with very severe disease and widespread articular deformities. Often it is a localized process limited to skin, with purpura or ulcerations. Peripheral neurological involvement can occur usually in the form of mononeuritis multiplex. Visceral involvement is rare, but can cause myocardial infarction or visceral perforation.

Pulmonary disease - Lung involvement is not uncommon in RA, with pleuritis being the most frequent finding. Fibrosis and nodular lung disease are occasionally observed.

Cardiac disease - Pericarditis, usually asymptomatic, is often an autopsy finding. Myocarditis, coronary arteritis and granulomatous disease are not common features, but are sometimes observed.

D. Course

The course of RA varies from patient to patient. Nevertheless, the majority of cases can be classified in one of two groups: those having a fluctuating or remittive course, with variable periods of milder disease, and those with chronic and often progressive arthritis. Some patients however, may experience a single episode of arthritis lasting months or a couple of years, and remain in remission thereafter, for documented periods of time of as long as 30 years *(234)*. Some other patients may have typical palindromic rheumatism but experience one or more isolated episodes lasting a few months, and thus comply with the diagnostic criteria for RA.

2.2 RADIOLOGICAL FEATURES

(12, 132, 162, 230)

The early radiological changes in RA consist of radiodense periarticular swelling and juxta-articular osteoporosis that occurs from reabsorption of subchondral bone. As the disease advances, articular erosions develop, most often in the edges of the articular cartilage and bone. These erosions may progress to severe articular destruction. Joint space narrowing is also a common finding, caused by loss of cartilage on the surfaces of the joint. The rate with which erosions occur varies among patients. Erosions have been reported within the first year of disease. Some patients however, particularly those with long remissions, may never develop erosive disease. Radiological damage can be considered a sign of disease progression. Patients with early erosions appear to have more aggressive disease in the long term. The rate of occurrence and frequency of erosions in RA are still under discussion. Most studies have been done in tertiary centers and show a large percentage of patients with radiological evidence of damage occurring within a few years *(56, 136, 222)*. Yet, in all probability, a referral bias exists in these series, with patients with severe disease being followed more often in those centers and with a higher probability of being selected in follow-up studies. Nevertheless, for those patients that are eventually going to have a severe course, radiological erosions develop early in the course of the disease, probably within 2 years *(92)*. A variety of factors have been related to the severity of radiological damage and will be discussed in more detail in the next chapter.

2.3 LABORATORY FEATURES

(3, 4, 12, 15, 99, 201, 132, 162)

A. Hematologic changes

Chronic normochromic normocytic anemia is common in RA, usually during periods of active arthritis. Leukocytes are usually within normal range, although they also may be elevated during periods of disease activity. Leukopenia is rare but occurs in conjunction with Felty's syndrome *(235)* (a variant of RA combining leukopenia, splenomegaly, vasculitis and repeated infections). Thrombocytosis is common in severe disease *(118)*.

B. Acute phase reactants.

The erythrocyte sedimentation rate (ESR) is the most frequently used laboratory test to assess inflammatory activity in patients with RA. In general, it parallels the disease activity, usually becoming normal during periods of remission. For this reason, ESR is often included as a criterion to evaluate remission in patients with RA.

C-reactive proteins and electrophoresis of serum proteins have also been used in the assessment of disease activity. Some studies have suggested that these methods may be more sensitive than the ESR to changes in disease activity; however, most clinical studies include the ESR as the sole acute phase reactant because of its simplicity and low cost.

C. Rheumatoid factors

Rheumatoid factors (RF) are antibodies directed against antigenic determinants on the Fc fragment of the immunoglobulin G. They can exist in all of three major classes of immunoglobulins (G,M & A). However, the most commonly used tests for RF (latex fixation or sheep cell agglutination tests) only detect IgM RF. Rheumatoid factors are present in the serum of 60 to 80% of the patients with RA. They are not specific for RA and can occur in many diseases including other connective tissue disorders and chronic infections, as well as in a small proportion of healthy individuals. Nevertheless, they have been extensively studied in relation to the role in the pathogenesis of the disease and also in relation to severity and prognosis.

D. Antinuclear antibodies

Antinuclear antibodies (ANA) detected using rat liver substrate have been detected in varying frequencies in different series, ranging from 14 to 60%. Some of these studies suggested an association with more severe disease and with sero-positivity for RF.

E. Other autoantibodies

LE cells have been found in approximately 10% of patients with RA. Autoantibodies characteristic of systemic lupus erythematosus such as anti-DNA and anti-Sm are almost invariably absent. Antibodies to extractable nuclear antigens (ENA) are occasionally found. Anti-SSA and anti-SSB also can occur particularly in association with Sjõgren's syndrome.

3. TREATMENT OF RHEUMATOID ARTHRITIS

(12, 35, 132, 162, 186)

The treatment of RA has traditionally been based on the sequential administration of different types of drugs and therapies. This can be illustrated by the therapeutic pyramid (Fig 1.1). The base of this pyramid consists of patient education and physical therapy, followed by the administration of non-steroidal antiinflammatory drugs (NSAIDS). As the disease progresses, if no significant beneficial effects are observed the so called second line drugs or remittive agents are administered. Corticosteroids, such as prednisone have often been added at this point, though their role remains highly controversial *(206)*. Other forms of therapy such as intraarticular steroid injections and surgery are also used, as required, at any point during the course of the disease.

3.1 PATIENT EDUCATION

(12, 13, 77, 132, 141, 162)

As is the case for most chronic diseases, patient education becomes an important issue in the management of patients with RA. Patient education should start once the diagnosis of RA is established and should continue throughout the course of the disease. Information can be provided not only by physicians but also by other members of the arthritis care team such as physical and occupational therapists, nurses and social workers. Education can be provided in a variety of ways ranging from informal talks with the health professionals to complex educational programs where different topics are covered in structured formats.

3.2 PHYSICAL THERAPY AND REHABILITATION

(12, 132, 162, 271)

A variety of physical and rehabilitation therapies have been used in the treatment of RA. Although they may not alter the biological course of the disease, these techniques play important preventive, palliative and corrective roles. They are used with a variety of specific objectives which include: pain relief, preservation and/or restoration of the articular range of motion, increase of muscular strength and endurance and preservation and improvement of functional capabilities. Several rehabilitative therapies are used which include:

Exercise therapy - the purpose of these exercises is to improve the muscle strength and the range of joint motion.

Occupational therapy - occupational therapy includes a variety of techniques: splinting, assisting devices, and activities of daily living training. Its main purpose is to increase function and quality of life as related to the activities of daily life.

Physical therapies - thermal modalities such as hot packs, paraffin and hydrotherapy have a relieving and soothing effect on patients. Ultrasound is often used as a 'deep heating' modality. Cold therapy is also occasionally applied and appears to be effective in providing some symptomatic relief. Whether this translates into any long-term benefits is unknown. Other techniques such as transcutaneous nerve stimulation, laser therapy and iontophoresis have also been recommended. The advantages and effects of these techniques remain to be proved.

3.3 NON-STEROIDAL ANTIINFLAMMATORY DRUGS

(12, 89, 132, 162)

Non-steroidal antiinflammatory drugs are usually the first medications prescribed for the treatment of RA. Several different NSAIDS, belonging to various chemical groups, currently are being marketed around the world and include drugs such as aspirin, naproxen, piroxicam, indomethacin and may others. These drugs have an important antiinflammatory effect thought to be mediated primarily through the inhibition of prostaglandin synthesis. In general, all these drugs appear to have comparable efficacy in the treatment of RA. Although there are individual differences in tolerance, response and preference, these appear to be lost in the overall statistics. The main clinical effects of these drugs relate to the improvement in the joint pain, stiffness and swelling experienced by patients with RA, which occurs within days of starting the therapy. Yet, the long-term effect of these drugs in controlling the disease is unknown. In theory, sustained suppression of inflammation could decrease the articular damage. However, there is no evidence so far that NSAIDS can slow the rate of joint destruction. Long-term controlled studies are unfeasible since almost every patient with RA requires NSAIDS for symptomatic control during periods of disease activity and the use of a placebo would be intolerable by the patient and probably unethical. Nevertheless, it is clear that these drugs alone are not enough to control the disease activity in the majority of patients and any potential effect they may have has to be small. In general, these drugs are considered to be useful in the symptomatic management of patients, but are not believed to alter in a significant fashion the natural course of the disease.

3.4 STEROIDS

(12, 20, 132, 162, 206)

Glucocorticoid therapy for RA was introduced in the 1950's. The dramatic antiinflammatory effect of these drugs was promptly recognized. Soon however, it was clear that the effectiveness of the steroids was accompanied by an equally dramatic toxicity. The role of steroids has been under discussion for the past decades. Some proponents of low-dose steroids recommend their use as soon as the disease can not be controlled with NSAIDS. Others, only use them as a very last resource.

3.5 SECOND-LINE DRUGS

(12, 89, 130, 132, 162)

Second-line drugs are also known as 'remission inducing' or 'disease modifying antirheumatic drugs' (DMARDS). In the pyramidal approach, second-line drugs are used when the response to NSAIDS is less than satisfactory. These drugs are thought to have a more profound effect, modifying the natural course of RA. The lag period for their clinical effects is longer than for NSAIDS, usually several weeks or months. These drugs do not have direct analgesic and symptomatic relief effects. Their precise mechanism of action is unclear. In general, it is believed that they interfere with different physiologic pathways (according to the drug considered) which affect the immunologic and inflammatory systems, and can lead to eventual control of some of the pathogenetic mechanisms present in RA. The disease activity parameters may improve or remain unchanged with second-line drugs, while with NSAIDS therapy alone there is continued disease progression.

Several drugs can be considered in the second-line group, the most common being: gold salts, antimalarials, d-penicillamine, sulfasalazine, azathioprine, methotrexate, cyclosporin A and some cytotoxic drugs. Individual responses to the different drugs are highly variable and overall statistics are generally not useful in predicting response in a given patient.

Toxicity for these drugs is high, and unfortunately limits the long-term use of these therapies. After a few years, most patients have discontinued the prescribed drug, due to either toxicity or inefficacy *(78, 104, 243, 284)*.

A. Parenteral gold salts

Parenteral gold salts as a treatment for RA were introduced by Forestier in 1935. He reported an improvement in 70-80% of treated patients *(86, 131)*. Since then, several studies have confirmed the beneficial effects of gold in RA *(70, 131, 179, 237)*. Yet, the response rates appear to be somewhat smaller, since improvement also occurs with the administration of placebo. This is due to the remittive nature of RA in many patients. The frequency of remissions with gold salts is not well established. Differences in study designs and study populations may account for some of the variations reported. Overall, around 20-30% of patients included in trials experience marked improvement and another 20-30% have a partial response. A proportion of patients will never respond to gold despite continued treatment.

Several parenteral gold compounds have been used and have proved to be similar in efficacy. They include gold sodium thiomalate (GSTM), aurothioglucose and gold sodium thiosulfate.

The major disadvantage of parenteral gold salts is their toxicity. Side effects have ranged from 5 to 80% in different series. The most common adverse reactions are dermatologic and include dermatitis, stomatitis and pruritus, accounting for 60-90% of all side effects. Renal effects are also relatively common with proteinuria occurring in approximately 5 to 25% of patients. Hematologic disorders include eosinophilia, leukopenia, thrombocytopenia and bone marrow aplasia. The latter, although infrequent, is the most serious complication of gold therapy since the mortality rate is high.

Unfortunately, although parenteral gold appears to be an effective drug in the treatment of RA, its toxicity limits considerably its use. Thus, the overall effectiveness may be low, since a significant proportion of patients have to discontinue the therapy before any clinical effects are evident. Another major disadvantage relates to its administration route. Parenteral gold salts are administered during the first months of therapy every week, via intramuscular injections. Hematologic and renal monitoring is necessary before each dose. Although the injections can be spaced out later on, many patients discontinue therapy because of the inconvenience in the administration schedule. Sambrook et al *(216)* reported that only 16% of patients continued to receive gold injections after 4 years. Richter et al however, reported better results with 50% of the patients continuing gold therapy after 5 years *(214)*.

B. Auranofin

Auranofin is a triethylphosphine gold compound that, as opposed to parenteral gold salts, can be administered orally *(21, 43, 48, 82, 170, 217)*. Auranofin was marketed in the early 1980's. Initial studies suggested an effect comparable to parenteral gold, with decreased toxicity. Some recent studies however, suggest that the efficacy of auranofin may be somewhat less than that of parenteral gold salts. Although, serious side effects are rare, diarrhea is a very common adverse reaction that limits its use in some patients.

C. Antimalarials

Antimalarials used for the treatment of RA are derived from the quinine compound. Two drugs are currently being used in North America: chloroquine and hydroxychloroquine, which are both administered orally. Antimalarials appear to have a beneficial effect similar to gold salts in placebo-controlled trials. Yet, long-term observational studies suggest that discontinuation for lack of benefit may be more frequent for chloroquine compounds *(214)*. Overall however, fewer terminations occur *(115)* than for gold. This can be attributed to the low toxicity of these drugs. A variety of adverse reactions can occur during therapy with antimalarials. However, most of these are self-limited and transient and include mild gastrointestinal and dermatological reactions. Neurological reactions are usually mild but occasionally, neuromyopathies and a myasthenia-like syndrome are observed. These effects are reversible after discontinuation of the drug. Ocular toxicity is reversible if the changes are limited to corneal deposits. Patients receiving large daily doses are at risk of developing retinopathy which eventually may lead to loss of vision. This reaction however, is easily monitored with periodic eye examinations.

D. D-penicillamine

D-penicillamine is an oral compound derived from the penicillin molecule. Its efficacy for the treatment of RA was first established in the early 1970's in a British multicenter trial *(113, 177)*. It has been shown to have therapeutic benefits similar to gold *(14)*. Toxicity for this drug is severe and frequent which somewhat limits its clinical use. Mild to moderate side effects include dermatologic reactions such as rash and stomatitis, loss of taste and nausea. Proteinuria has been reported in up to 20% of the patients, in some cases leading to nephrotic syndrome *(125)*. Hematologic reactions are the most serious effects and include leukopenia, thrombocytopenia and aplastic anemia. As with the gold salts, periodic monitoring of laboratory parameters is necessary.

E. Sulfasalazine

Sulfasalazine is an oral drug that has been traditionally used in the treatment of inflammatory bowel disease. Within the past decade its beneficial effects in RA have become apparent *(203, 255)*. In general, its clinical efficacy appears to be similar to that of other second-line drugs, with similar withdrawal rates. Adverse reactions, although frequent, are not as serious as those observed with gold and penicillamine treatments.

F. Low dose methotrexate

Although methotrexate is an antimetabolite, its role in the treatment of RA should be considered separately. As a treatment for RA, methotrexate is given in low doses, either orally or parenterally *(249, 277)*. Controlled trials have shown a therapeutic effect that begins earlier than for other second-line drugs, usually within a few weeks. It appears that its efficacy is partially mediated through antiinflammatory mechanisms which would explain why its action starts relatively soon after initiating therapy. Efficacy appears to be similar to that of parenteral gold *(251)*. The main concerns in the use of methotrexate in the long-term are related to its potential hepatotoxicity. It would appear however, that although mild enzymatic changes are common, serious symptomatic liver involvement is very rare and has been estimated to be less than 1 per 100,000 patients treated *(89)*. Periodic non-invasive monitoring is required. The role of liver biopsies at given intervals is still under discussion.

G. Other antimetabolite/cytotoxic drugs

Several other anticancer drugs besides methotrexate have been used in the treatment of RA. Of these, the most commonly used are azathioprine and cyclophosphamide. Both have been shown to be effective for RA. Yet, clinical and experimental experience with these drugs is less than for other second-line compounds. In general, these drugs are used after several other remittive drugs have been proven ineffective. Toxicity is a major concern for all cytotoxic drugs and their efficacy does not appear to be superior to that of other remittive agents.

H. Combination therapy

Several studies have reported the effects of combining one or more of the above drugs *(22, 23, 52, 75, 98, 116, 124, 159, 161, 163, 184, 204, 221, 236, 277)*. Yet, there is not sufficient evidence to support that this form of therapy is advantageous, and the indications for its use are controversial.

I. Experimental therapies

A variety of other therapies have been proposed for the treatment of RA, that remain at experimental stages *(133)*. These include drugs such as cyclosporin A, monoclonal antibodies against T lymphocytes and cell receptors, cytokine inhibitors and total lymph node irradiation. These therapeutic modalities have been used only in severe, refractory cases, and their generalizability to the general population of patients with RA is not clear.

3.6 INJECTIONS OF JOINTS AND SOFT TISSUES

Intraarticular and soft tissue injections of corticosteroids have been used in the treatment of RA for several decades. The fast response and palliative and antiinflammatory effects of this form of therapy are well recognized. In RA however, the effects are generally short-lived and there is no evidence whatsoever that they alter the underlying disease.

3.7 SURGERY

The management of many patients with RA may eventually require surgery. Some of the most commonly performed surgeries include: release of nerve entrapment (most often the median nerve in the carpal tunnel syndrome), synovectomies, tenotomies to improve tendon contractures and range of motion, arthrodeses and arthroplasties.

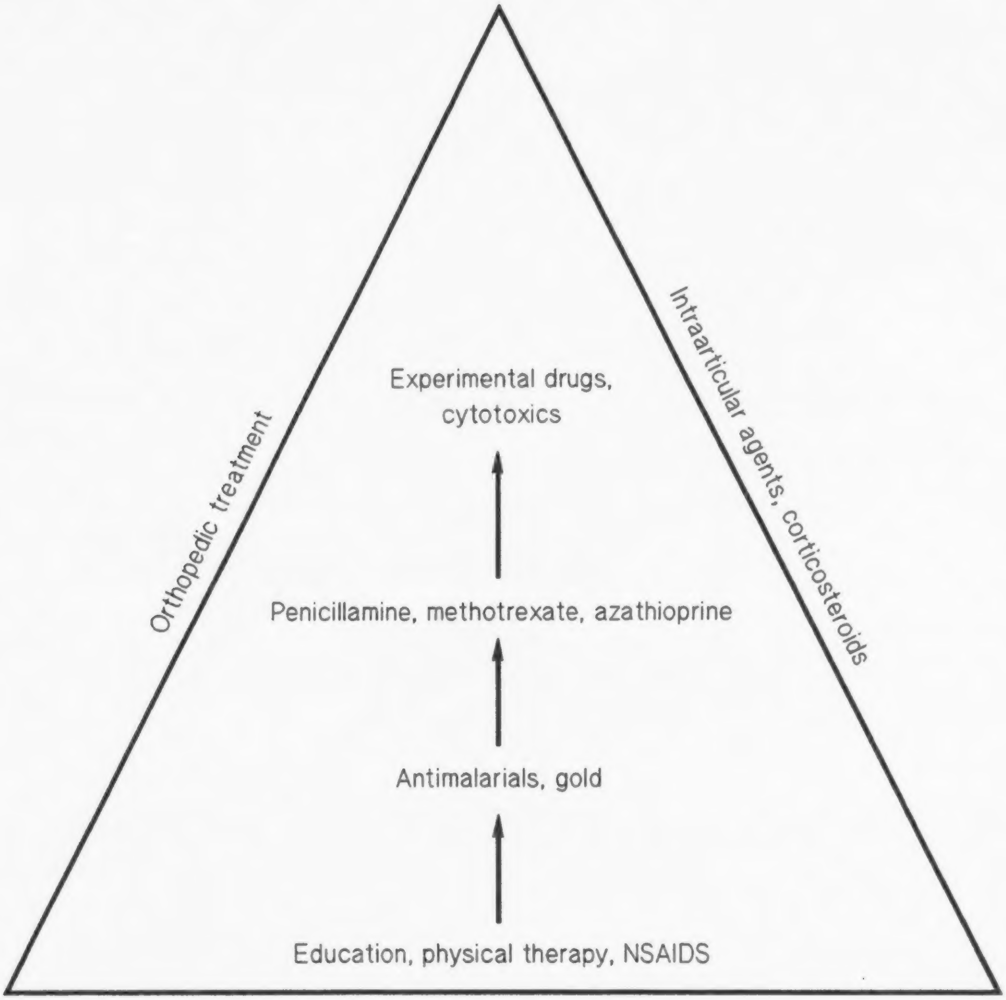

Experimental drugs,
cytotoxics
Penicillamine, methotrexate, azathioprine
Antimalarials, gold
Education, physical therapy, NSAIDS
Orthopedic treatment
Intraarticular agents, corticosteroids

Figure 1.1 Treatment pyramid for Rheumatoid Arthritis

(adapted from reference 12)

CHAPTER 2

REVIEW OF THE LITERATURE:

OUTCOME IN RHEUMATOID ARTHRITIS

The outcome of RA has been the subject of controversy. The initial perception, decades ago, was that RA was a chronic crippling disease with an extremely poor prognosis. As the first follow-up studies were published, it appeared that the outcome was not as ominous, with common spontaneous remissions, and a marked number of patients not only not deteriorating, but improving their functional status *(62-64, 233, 234)*. Recent studies, starting in the 1980's have again reversed this viewpoint, suggesting that RA may be a more 'malignant' disorder than previously recognized *(193, 198, 288)*. One of the major problems in sifting data from all the different studies is the widespread variation in the clinical settings where the samples were collected and the disparity of methods used. Furthermore, the most cited publications span decades, that have seen major changes in the way patients are treated (e.g. corticosteroids and second-line drugs) as well as in the general social conditions and access to health care.

Another issue is the choice of parameters to measure outcome *(8, 79, 88, 164, 165, 245)*. Outcome in RA can be evaluated from a variety of perspectives including clinical examination of the joints, laboratory and radiological tests, and evaluations of functional capacity. Although interrelated, these measurements probably represent various dimensions of the overall clinical status of patients. Outcome studies using different endpoints should not be compared then, at the same level, since they represent different aspects of a construct.

1. OUTCOME MEASURES

1.1 DISEASE ACTIVITY

Several clinical and laboratory parameters have been used to follow-up articular inflammation and disease activity in RA.

A. Clinical assessment of disease activity

The clinical assessment of disease activity includes a variety of measurements designed to detect differences in the degree of articular inflammation and accompanying symptoms, such as pain or stiffness *(66, 67, 266)*. Some of the most commonly used measures and indices include:

- *Duration of morning stiffness* - Morning stiffness is a prominent feature of RA and usually correlates well with articular inflammation.

- *Evaluation of pain* - Pain can be evaluated using a variety of methods which include visual analogue scales, ordinal scales or more detailed questionnaires. These instruments are sufficiently reliable for the evaluation of pain. Pain, however, is not that reliable in the prediction of disease activity. Often, severe pain is related to architectural damage, without inflammatory activity. Furthermore, the pain threshold is highly variable among individuals and patients with widespread articular inflammatory disease and mild pain or absence of pain are not unusual. The evaluation of overall pain is important in relation to patient comfort and quality of life but is not a very precise measure of disease activity. More specific are the joint indices reviewed below, that incorporate pain or tenderness in the various joints in the final measure.

- *Joint counts* - A wide variety of joint counts have been proposed to evaluate articular activity *(135, 215)*. Some are based on pain and tenderness in the different joints, others on the presence of articular swelling. Several indices are weighted according to the severity of the pain, tenderness or swelling. The number of joints that should be included is also controversial. While all indices appear to have adequate validity and reliability, some researchers prefer indices with a higher number of joints evaluated to be able to detect small changes. Others propose the use of counts of fewer joints and offer 2 advantages: simplicity and increased reliability by lowering the potential for measurement error. Overall, the majority of indices used appear to be adequate to measure disease activity and are particularly useful for the evaluation of clinical trials.

- *Patient and clinician global impressions* - These measurements are usually ordinal scales and are best suited to evaluate a change in patient status (e.g. improved, unchanged etc). They are most often used in clinical trials.

- *Other* - Many other instruments have been proposed to evaluate disease activity, including grip strength, and PIP circumference. These measurements are best evaluated in comparison to a baseline value, and are thus more useful to evaluate change than to provide an overall measurement of patient status in relation to disease activity.

B. Laboratory assessment of disease activity

Several laboratory parameters have been used to monitor disease activity in RA *(4, 132, 162)*:

- *Acute phase reactants* - The ESR has been the most commonly used laboratory test to monitor disease activity. It correlates significantly with joint counts, and it has been suggested that persistent high values are associated with radiological damage *(7, 222,* *259)*. Sherrer et al *(232)* also reported a positive correlation between ESR and functional outcome. Others, however, *(76, 123, 160)* did not find a correlation between ESR values at onset and outcome. An explanation for these variations may be that consecutive readings may relate to outcome, but isolated determinations do not provide a reliable measure of long-term prognosis *(63)*. Other acute phase reactants such as C-reactive protein, plasma viscosity, protein electrophoresis and immunoglobulin subtype concentrations also have been related to disease activity. However, from a practical point of view, they do not offer clear advantages over the ESR.

- *Hemoglobin concentrations, and other markers for anemia* - Chronic anemia is a common feature of RA and often reflects active disease. It has been used, as the ESR, to monitor the degree of disease activity, and has been related to poor prognosis *(244)*.

- *Rheumatoid factors* - High titres of RF have been associated with more severe disease *(46, 76, 127, 160, 183, 205, 209, 211, 223, 232)*. However, fluctuations of the titre in individual patients often do not reflect the changes in articular inflammation. As such, they are not sensitive or specific enough to monitor disease activity, although they may be markers for overall long-term prognosis.

Many of the measures of disease activity are commonly used in clinical trials comparing different therapeutic modalities *(8)*. In general, they are sensitive to the changes that occur in the short term, when compared to baseline measurements. Their role in the assessment of long-term outcome is not as conclusive. Some of the indices, particularly those measuring pain, may reflect temporary symptoms and not parallel the underlying patient status. Nevertheless, continuous joint activity and pain during the course of RA has been associated with a poor functional outcome *(63, 108)*. Others, however, found this relationship inconsistent *(232)* with positive associations for some of the indices but not for others. Sharp et al *(225)* and Scott et al *(222)* also reported an association between the indices of disease activity and the development of joint erosions. Yet, it also has been reported that 10% of the patients without clinical synovitis and considered inactive will have radiological deterioration *(120)*.

1.2 RADIOLOGICAL DAMAGE

Radiographic changes are the direct effect of joint destruction. The radiological assessment of patients with RA provides an accurate tool to measure disease progression and articular damage. As opposed to measures of disease activity, radiological changes represent a more stable picture of the clinical status of the patient, in relation to joint damage. This is so because once the radiological damage is established, very seldom will it revert to a previous stage. Radiographic abnormalities have also been related to other outcome and clinical measures *(28, 289, 296)* such as limited joint motion *(56)*, deformities *(56, 93, 226)*, joint counts *(93, 226)*, ESR *(54, 56, 222)* and RF *(56, 220, 225)*. The relationship between radiological damage and functional disability is not as clear. Several investigators *(65, 190, 212)* found no association between functional status and changes in hand radiographs. Others have reported no relation between clinical parameters and radiological progression *(119)*.

Several methods have been proposed to measure radiographic changes. The first dilemma relates to the choice of joints to be evaluated *(228)*. Most often, radiographs of the hands are used for assessment *(228-230)*. A good correlation has been found with radiological changes in other joints *(222)*. Several techniques have been developed to score hand radiographs. Various methods include different numbers of joints read and techniques *(87, 97, 105, 137, 222, 229, 230, 261)* but, in general, there is agreement that the critical observations are the joint space narrowing and the erosive changes *(87)*. One major advantage of radiological scoring is that the radiographs can be blinded, providing the necessary objectivity to avoid diagnostic or expectation bias in reading them.

1.3 FUNCTIONAL STATUS

Functional status is determined by the ability to perform the activities of daily living. One of the most relevant aspects of the outcome of RA is the effect of the disease on functional capabilities *(90, 260)*. The ability to function normally has a major bearing on quality of life and social adaptation. The physical impairment observed in RA is a major concern for patients and caregivers since eventually it shapes all facets of life, including among others, employment, social and family life, and psychological well-being. It also has a major economic impact on the individual patient and society as a whole. For these reasons, functional disability is fundamental to the overall prognosis of a patient with RA. Several instruments have been developed to measure physical function. The majority of these tools are based on the performance of everyday activities. In general, the different instruments fall into one of three categories *(260)*:

A. Measures based on clinical judgement

The most classical measure in this group is the Steinbrocker functional index which has 4 grades *(249)*:

I. Fit for all activities.

II. Moderate functional restriction (adequate for normal activities, despite limited motion in one or more joints).

III. Marked restriction (limited only to self-care).

IV. Confined to chair or bed.

This index has been widely used in rheumatology. It is attractive for its simplicity, but is highly subjective and does not offer sufficient variability to detect small or even moderate changes.

B. Measures based on observed performance

Several instruments have been developed within this category. These include among others *(5, 199)*:

- Button test, which measures the time necessary to button and unbutton a button board.

- Walking time, which records the walking time for given distances

- Grip strength, measured with specially adapted manometers.

C. Self-reported assessments

These assessments are based on questionnaires regarding functional status *(5)*. Some are completed by the patient with no assistance and others are interviewer-administered (i.e. filled by an interviewer questioning the patient). Very often, these questionnaires are part of broader instruments that assess a variety of dimensions in the health status of patients. These health status questionnaires include a variety of areas such as functional status, pain, patient satisfaction, social adaptation, psychological status and global outcomes. The AIMS questionnaire (Arthritis Impact Measurement Scales Health Status Questionnaire) was one of the first instruments designed to assess health status in patients with arthritis and has been repeatedly validated *(166)*. A new version has been developed recently (AIMS2) *(167)*. The HAQ (Stanford Health Assessment Questionnaire) is another modern instrument that has been widely used for the assessment of patients with RA *(286)*. It also has high reliability and validity. The disability scale is one of the six dimensions of the HAQ, and covers most aspects of daily living. Other commonly used instruments include the MACTAR (McMaster Toronto Arthritis) and SIP (Sickness Impact Profile) *(5, 262)*. The scores obtained from these questionnaires appear to be highly correlated although some variations are observed for certain dimensions. A major obstacle to the systematic use of these questionnaires in clinical settings is that they are time-consuming and take about 15 to 20 minutes to complete. For this reason, a shortened version of the disability component of the HAQ instrument (MHAQ-ADL) has been developed *(195)*. This concise version also has shown adequate validity and reliability.

Functional capacity often has been found to be associated with parameters of disease activity such as pain and joint counts. The relationship with radiological changes is unclear. Some studies have not found any significant associations *(65, 190, 212)*

1.4 MORTALITY

Rheumatoid arthritis is generally considered a non-fatal condition. Yet, several studies have reported increased mortality rates in patients with RA *(1, 188, 191-194, 197, 254)*. In general, the distribution of causes of death is similar to that of the general population although a small proportion of the deaths is secondary to complications of

RA or its therapy *(174, 178, 213)*. Independent associations of mortality with duration of disease, functional disability, seropositivity for RF, and joint counts have been reported *(145)*. Pincus et al found a significant effect of some of the above variables plus various measures of functional status and formal educational level *(191, 194, 196)*.

1.5 OTHER

Many other measures included in the health status questionnaires reviewed above have also been used as outcome criteria *(4, 59, 148, 165, 168)*. They include variables such as overall well-being, psychological status and quality of life. Another important aspect is the measurement of the economic impact and the effects of the disease on occupation and job performance *(154, 157, 169, 293, 294)*.

2. OVERALL PROGNOSIS: REVIEW OF LONG-TERM STUDIES

Several studies have reported the outcome of RA at different stages in the course of the disease *(6, 38, 62-64, 73, 191, 207-211, 213, 220, 223, 225, 231-234, 244, 264, 265, 291)*. The majority of these series have included patients with a follow-up of less than 5 years. Long-term studies have been sparsely published over the past 50 years and often are not comparable given the differences in patient selection and outcome measures. Some of the larger and longest studies were published in the 1950's and 60's.

Short et al, in Boston, studied 250 consecutive patients hospitalized for RA in the late 1930's and observed for several years *(233, 234)*. The only treatment received by these patients was rest, analgesics and physical therapy. Eighty percent were followed for a minimum of 5 years. One hundred and thirty (53%) were followed for at least 11 years and, in some cases for up to 17 years. Fifteen percent of these were in remission, 51% had slight to moderate improvement and 34% had deteriorated. The most striking factor in determining prognosis was the duration of disease. Three-quarters of those patients with arthritis of less than a year's duration improved and 37% achieved remission. Relapses, however, were frequent. Although it was ultimately concluded that about 50% of patients would improve after 10 years, these results were based on only slightly more than half of the originally included patients.

Bywaters et al followed 250 patients with RA, 125 with a disease duration of 1 year or less *(38)*. The first follow-up report was at 10 years. At that point, close to 40% of the patients had an adequate functional capacity. In a subsequent follow-up, more than half of the patients were dead. In those that died, there had been a preceding decrease in functional capacity. This however, was not necessarily from a cause related to RA.

Duthie et al, in 1964 *(63)*, reported a follow-up study of 307 patients that had been hospitalized for RA, in Edinburgh, UK. The mean duration of disease at entry had been over 6 years and none of the patients had been on DMARDS. After 9 years of disease, the functional capacity of the 200 patients remaining in the study had improved: 62% of the patients were in Steinbrocker's functional class I or II compared to 35% at entry.

Scott et al, in the UK *(223)*, reported the outcome of 112 consecutive patients included in a follow-up study between 1966 and 1968. All patients had severe disease and were admitted to hospital, treated by bed rest followed by a combination of chloroquine, gold and prednisolone. Withdrawals from gold were treated with penicillamine or cytotoxic drugs. During the first 10 years an improvement in the functional capacity was observed, but after 20 years, the majority of patients were either dead (35%) or severely disabled and only 18% were in functional class I or II.

Two studies of patients, initially seen within a year of onset and followed after 20 years, also reported a high percentage of patients either dead or markedly disabled *(209, 213)*.

Recent follow-up studies at Vanderbilt University by Pincus et al have shown a gloomy prognosis for individuals with RA, with mortality rates in severe patients similar to that of triple vessel coronary disease and Hodgkin's lymphoma *(191-194, 197)*. These studies, however, were conducted in a tertiary referral center and the patients included already had a somewhat long duration of disease, which suggests that the selection was biased towards severe cases. A similar study by Wolfe et al found that half of the patients with RA would reach severe degrees of functional impairment 10 years after the initial visit to the clinic *(283, 288)*. The study also concluded that outcome could be predicted by demographic characteristics and clinical assessments including global severity and pain.

A Canadian study by Sherrer et al *(232)*, on 681 patients with a mean disease duration of 10 years and a follow-up of 12 years suggested that disability and radiological progression occurred during the first 10 years of disease, with patients stabilizing thereafter. Only 10% in their study, however, did not develop significant incapacity.

Some other studies have reported a much better prognosis for RA, with patients maintaining an adequate level of functioning after several years of disease. Capell et al reported 123 patients, 75% of whom were followed for 10 years showing significant improvement in various disease activity parameters *(44)*.

Various short-term studies of 2-3 years duration have been published *(27, 45, 65, 83, 84, 136, 208, 211, 267, 268)*. Many of these reports have been useful in establishing the rate of development of radiological damage in RA, since these changes rarely improve. Masi et al *(160)* reported 50 patients with RA of recent onset, followed for a mean duration of 3 years. At last follow-up, functional capacity had remained unchanged or improved in most patients. Fifty percent of the females followed radiologically had normal X-rays. In contrast, some recent studies estimate the frequency of development of erosions within the first 2-3 years to be as high as 80 to 90% *(92, 156, 174)*. In these short-term studies, because of the remittive nature of RA particularly in the first years, it is difficult to extrapolate the other clinical parameters of disease activity and function to the long-term prognosis.

3. PROGNOSTIC FACTORS

3.1 AGE

Short *(233)* found a larger number of improvements in the group of patients under 40 years of age. Although he reported no differences in the duration of disease between younger and older patients, the analysis was not controlled for this variable.

In the initial study by Sherrer et al *(232)*, and in a subsequent multicentre study including patients from the US *(231)*, age was the strongest predictor of disability, after adjusting for other factors.

Although these and other studies have shown an association between age and poor outcome *(85, 127, 223)*, the outcome measures selected have usually been functional scores such as the HAQ that are not adjusted for age. It is clear that even in healthy populations, age is related to a decrease in function.

No effect *(31, 256)* or a more favorable outcome in older patients also has been reported in several studies *(47, 50, 57, 69)*. It has been suggested that some of these patients may have a benign subtype of RA, or a different disorder altogether. Occasionally, the onset in these older patients is acute, which has lead to the name 'acute synovitis of the elderly'. It is likely that many of the long-term studies based on prevalent cases may not have included these patients. These older patients also could die from other causes and be lost to follow-up which may explain some of the differences observed between short and long-term studies in relation to the effects of age on prognosis.

3.2 GENDER

Short et al, in their follow-up study of 250 hospitalized patients *(233)*, did not find significant differences in outcome between males and females, although the rate of improvement was slightly higher for men. Bywaters et al also reported a better prognosis in males *(38)*.

Several other studies *(63, 76, 132, 160)*, but not all *(85, 123, 205, 225, 257)* , also have reported a more favorable prognosis in men. On the other hand, severe seropositive nodular disease with systemic vasculitis, which is the most malignant form of RA, occurs more often in males.

3.3 TYPE OF ONSET

An acute onset has often been associated with a better prognosis in the long term *(38, 85)*. Several other studies have not been able to find any differences in the course of RA among patients with acute, subacute or insidious onset *(106, 123, 155, 211)*.

3.4 CLINICAL FEATURES

The pattern of joint involvement at onset appears to influence the eventual outcome *(132)*. Lower numbers of affected joints are related to milder disease. Early symmetrical involvement also appears to be a marker of poor prognosis *(39)*.

3.5 RHEUMATOID FACTOR

Rheumatoid factors have been extensively studied as prognostic factors. The majority of the outcome studies have shown a positive association with poor prognosis *(10, 38, 46, 76, 127, 205, 211, 223, 232, 281)*. In general, they have been correlated with parameters of disease activity such as joint counts and ESR, and also with radiological damage. The relationship to functional capacity is more controversial. Pincus et al did not find a significant association of RF with functional capacity *(190, 191)*, but others have *(232, 283)*.

3.6 ANTINUCLEAR ANTIBODIES

It has been suggested that ANA may be associated with severity. This association, however, may be spurious because ANA has been observed most frequently in seropositive patients who may be prone to more severe disease *(132)*.

3.7 HLA ASSOCIATIONS

The genetic associations of RA are well known. Its familial aggregation and HLA associations have been extensively studied *(102, 181, 238, 239, 272)*. Although the contribution of genetic factors is based on solid evidence, their overall influence appears to be controlled by the effect of yet unknown exogenous factors *(2, 240, 277)*.

The association of HLA DR4 with RA has been well established. Doubts remain as to whether DR4 is a marker for susceptibility, severity or both *(40, 100, 101, 103, 126, 182, 241, 250, 269, 273, 276, 295)*. It is certain that in most populations tested, DR4 is increased in patients with RA when compared to the background population. Some researchers have suggested that this increase is partially due to a selection bias. They argue that DR4 is a genetic marker for severity and that patients with more severe disease are more often selected for studies.

Several reports have compared DR4 positive and DR4 negative patients. The majority of these have evaluated the radiological changes in these patients. The results have been in conflict, with approximately half supporting an association with severity.

A plausible explanation for the variation of published results may be given by the study of extended DR4 haplotypes. It has been suggested that it is not HLA DR4 but the associated DQw7 allele which is responsible for increased susceptibility and/or severity in RA.

The most recent evidence has pointed to specific subtypes of DR4 as responsible for the observed association with RA *(279)*. Several different subtypes recognized by mixed lymphocyte reaction have been described for the different HLA types and severall alleles are included under DR4 *(95)*. The increased DR4 subtypes in Caucasian RA patients are Dw4 and Dw14. Recent work has shown that the association of DR4 with RA is given by some of the specific sequences encoded by the third hypervariable region of the DR4 ß-chain allele (HLA DRß1) *(58, 200, 279, 292)*, which are related to the subtypes Dw4 and Dw14. Some other HLA types, such as DR1 that share those sequences, also have been associated with RA. The HLA DRß1 allele also appears to have a different distribution in RF positive and negative individuals *(200)*. It seems then, that the relationship of RA to DR4 is valid only for some of the DR4s. This could explain some of the differences in the literature, if the proportion of DR4 subtypes or other epitope-sharing HLA types varied among the study populations.

3.8 THERAPY

The effects of therapy on the long-term outcome of RA are controversial *(94, 112, 128, 134, 184, 202, 219, 242, 258, 278)*. It is clear that most of the recommended second-line drugs have a beneficial effect in the short-term, as proven by placebo-controlled clinical trials. As a rule, however, the majority of patients will stop the drug they were receiving after a few years, very often for what they and their physicians consider a lack of effect.

Long-term controlled trials are not feasible in RA, since the drop-out and withdrawal rates are high after 1 year. The proportion of patients continuing therapy may no longer be representative of the initial sample, and the potential benefits of randomization cease. Furthermore, the addition of new drugs may confound the effects. Hence, eventually, the study becomes observational. Long-term observational studies, although controversial *(80, 107)*, have used a variety of techniques and outcome measures to evaluate efficacy and effectiveness. Most studies have focused on the effect of gold on the radiological progression of disease, but a few others also have been conducted for some of the other second-line drugs *(55, 132, 162, 203, 227, 263)*.

Results have been conflictive. However, it is clear that at least some of the studies have reported a reduction in the rate of radiological progression *(119)*. The design and methods in these reports are so different that comparisons and pooling of data would be difficult. Yet, the available evidence suggests that in all probability, in those patients showing a good clinical response, the radiological damage may be controlled or retarded.

Functional measures are often included in clinical trials of second-line drugs, and generally improve in the short-term. Few studies have reported the effect of these drugs on long-term disability. Epstein et al published a follow-up study in gold-treated patients showing no improvement in their functional capacity *(71, 72)*. The study however, had some methodological problems that may have influenced the results *(153, 158)*.

The role of surgery also plays a significant role in the functional outcome of patients with RA. A French study found that surgery was the single most important factor in the improvement of outcome in the long term *(6)*.

3.9 SOCIOECONOMIC FACTORS

A deleterious effect of low education levels on the prognosis of RA has been suggested in several studies. Pincus et al have published extensively on this subject, showing that patients with RA who have lower education levels are at increased risk for disability and RA-related mortality *(41, 189)*. Others also have reported this association *(144, 146)*. The relationship of income to disability has been documented in a few instances *(146, 169)*.

Marital status has been shown to be related to disability in patients with RA *(169)*. This association also occurs for other chronic diseases and for general mortality rates, with single, widowed and divorced individuals being at a disadvantage.

3.10 PSYCHOSOCIAL FACTORS

The impact of psychological and psychosocial factors on RA is still not well defined *(24, 25, 51)*. A close correlation has been shown for depression and other psychological variables and disability. In these cases however, it is difficult to establish the direction of the cause-effect relationship. Several studies have focused on the effect of 'self-efficacy' *(33, 152)* and 'learned helplessness' *(42)*, suggesting that the beliefs that patients have in being able to control their disease may have an impact on their health outcomes.

CHAPTER 3

RATIONALE AND OBJECTIVES OF THE STUDY

1. LIMITATIONS OF PREVIOUS STUDIES

Several methodological issues have to be considered in analyzing outcome studies in chronic diseases. In RA, the difficulties are even greater because of the fluctuating nature of the arthritis which may bias the selection and follow-up of patients. Many of the published studies have shown significant differences in the severity of the outcome in RA. These differences can be attributed, at least partially, to differences in design and methodological biases.

A. Patient selection.

Patient selection is in all probability the main determinant of the validity of an outcome study. All outcome studies should be based on the follow-up of an inception cohort, with patients identified at a uniform, preferably early, point in the course of their disease. In the particular case of RA, this ensures that patients in whom the disease goes into remission and are not followed-up by physicians are taken into account. Several approaches can be taken to select the inception cohort. Cases can be recruited from the following sources *(245)*:

1. Community survey - this source would include all possible cases; yet, the uncertainty of the diagnosis is considerable in these kinds of surveys.

2. General practitioner patients - this source would include the majority of patients with RA, mild as well as severe cases.

3. Rheumatologist patients - in this case a referral bias towards including patients with more severe disease could occur. This, however, would depend on several variables such as the characteristics of the practice (hospital or community based) and of the health system in place (universal health care access vs. other health care systems). Diagnostic certainty in this group would be high.

4. Hospital inpatients - these patients form a highly selected group and in general, have either severe disease or associated disorders. As such, they are not representative of the general population of RA patients. As an example, in the studies by Duthie et al *(62, 63, 64)*, all patients had been hospitalized because of severe disease and were included in the study at that time. When they were examined 9 years later, a marked proportion had improved their functional capacity. As a possible bias, the sample in this study may have been subject to a 'floor-ceiling' effect. These patients may have had such a degree of severity that given survival, the only likely outcome was improvement. Furthermore, if the initial measurements had some degree of random error, any new measurements could have been influenced by the statistical effect of 'regression to the mean' and repeated evaluations would have shown improvement.

The other major aspect in the selection of patients is the point in time in the course of the disease in which the sample has been assembled. The ideal situation is to include patients at onset, when the symptoms develop. This is not possible for some diseases where the diagnosis is sometimes based on accidental findings (e.g. diabetes), but is certainly feasible in RA, where the onset is marked by the beginning of symptoms. Studies that are based on the selection of prevalent cases such as outpatients coming for follow-up will probably overestimate severity since those patients with severe symptoms will consult more often, and will have a higher probability of being selected than those who are only sporadically seen.

The selection of an inception cohort is not only relevant in the description of the overall prognosis, but also has an important bearing in the associations with various factors. If the variables under study are in any way related to the selection process, inaccurate findings will result. For example, if the effect of sex is being studied, and males consult a specialist only when the disease becomes severe, the final result will be that males seem to have a worse outcome, when in reality a selection bias could have been responsible for this finding.

The majority of the long-term prognostic studies in RA have not been based on the follow-up of inception cohorts. Sherrer et al *(232)*, estimated they had included the majority of patients with RA followed by rheumatologists in the province of Saskatchewan at the time of the study, but the follow-up was based on prevalent cases at different points in the course of their disease. In general, the majority of studies have included prevalent cases selected from out-patient rheumatology clinics. Recent studies have incorporated multivariate analyses adjusting for the duration of disease. This adjustment controls the confounding effect of disease duration but has no influence on the bias resulting from the selection process. Studies reporting follow-up assessments of inception cohorts are usually short-term. Many of these studies, however, have been conducted in tertiary centers, and are subject to some degree of referral bias.

B. Duration of follow-up.

It is clear that the results of a 2-year study can not be compared to results of a 2-decade follow-up. The majority of the outcome studies in RA can be considered short-term (less than 5 years of follow-up) *(245)*. Long-term duration studies are few, and subject to loss to follow-up which makes the findings less reliable. Some long-duration studies have found a good prognosis at 10 years and significant deterioration at 20 years *(207, 209, 223)*. Since the proportion of patients lost to follow-up increases with the length of the study, a severity bias may be in place: patients with more severe disease are more prone to continue to participate in the study since they require more medical services. On the other hand, since the incidence of RA peaks at around the 5th decade, many of the patients will be dead after 20 years. This effect will be even more marked if the follow-up is based on prevalent cases. Although in some, death may be a consequence of arthritis, many others may die from other age-related causes, and their RA-related status and severity will remain unknown.

c. Choice of outcome measures and instruments

Follow-up studies in RA have incorporated a variety of instruments. As previously discussed, different categories of instruments measure different dimensions of outcome. No single measure provides a complete assessment and although the different indices are often correlated among themselves, their associations with prognostic factors frequently differ. Therefore, studies of similar populations of patients with the same length of follow-up may not be comparable if their outcome measures differ.

Also of major concern is the potential bias in the measurement of the outcome variables when the evaluation can not be blinded. For some indices such as the radiological scores or laboratory parameters, blind assessments are the norm and have been performed in most studies. The assessment of joint indices and functional capacity is more difficult to achieve. Although the examiner may be 'blind' to some features of the patient, bias in relation to some variables (e.g. sex or age) can not be avoided. An alternative, but partial, solution is the use of self-response questionnaires, given that the patient may be unaware of the direction of the risk effects under study. A major problem with self-response questionnaires is the fact that they are highly subjective.

For that reason, only those instruments that have been validated with objective standards should be used.

D. Sample size and power

The sample size of the study may be a major determinant of differences among publications. As the sample size increases, so does the probability of finding significant associations. Some of the discrepancies related to the effects of prognostic factors, particularly when no associations are found, may be a consequence of differences in sample size among studies.

E. Adjustment for confounders

The influence of confounding variables has been taken into account in most recent studies. However, similar studies often do not adjust for the same confounders and the final results may differ.

2. OBJECTIVES AND HYPOTHESES

The main objective of this study was to examine the clinical status and outcome in an inception cohort of patients with RA after 6 to 7 years of disease and to determine if the variability in severity among patients could be explained by some demographic, social and biological factors. For this purpose, the first step was the selection of the study cohort. An inception cohort of patients with RA with an onset of disease in 1985 was chosen as the study population and retrospectively selected. The specific objectives of the study were both descriptive and analytic.

2.1 DESCRIPTIVE OBJECTIVES

- To describe and quantify the clinical status and outcome in relation to disease activity, articular damage and disability in an inception cohort of patients with RA, after approximately 6 to 7 years of disease.

- To describe the use of second-line drugs in these patients, and rheumatologists' prescription patterns.

2.2 ANALYTIC OBJECTIVES

- To examine the relationship between specific biological, demographic and social factors and outcome in patients with RA.

- To quantify the risks of these different variables in relation to the different aspects of outcome (disease activity, articular damage and disability).

- To examine the relationship between early use of second-line drugs and outcome.

2.3 HYPOTHESES

The following working hypotheses were established a priori:

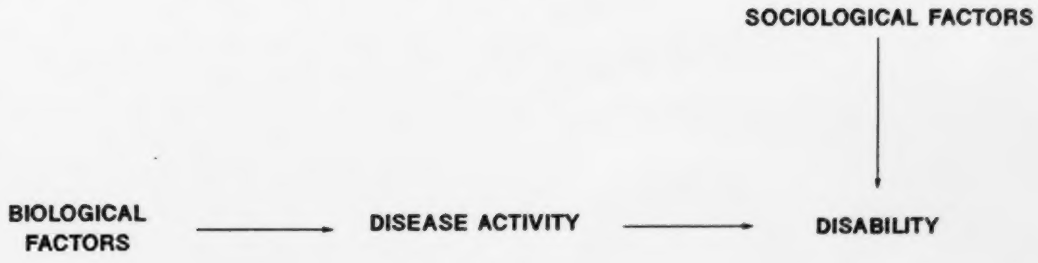
- Outcome in RA after 6 to 7 years of disease varies among patients according to the measures used (disease activity, articular damage, functional disability)

- Biological factors including the presence of HLA DR4 and RF, and demographic and social factors are independently associated with the clinical status of RA patients

- The associations vary according to the measure under consideration

A general model was proposed as a theoretical framework for the study of outcome in RA. It was hypothesized that the different categories of outcome measures were indicators of different latent concepts related to the overall clinical status. Functional status could be partially explained by the effect of disease activity and external socioeconomic factors.

The following is a simplified diagram of the general theoretical model:



3. RELEVANCE OF THIS STUDY

Most studies related to the outcome of RA are not based on the follow-up of inception cohorts and are thus subject to bias. The aim of this proposal was to study the clinical history of treated RA and to determine if any factors account for the variability observed among patients. The fact that this study was conducted in an inception cohort of incident cases allowed for the examination of patients at the same temporal stage of disease. Canada's National Health Act provides universal health services and hence, facilitates more equitable access to medical care than countries such as the United States of America where the majority of outcome studies in RA have been conducted. Thus, the relationship of education and socioeconomic status on disability can be better evaluated than in United States-based studies, where access may be restrained and patients in the lower socioeconomic stratum may consult a rheumatologist only when the disease becomes severe.

In summary, this study was necessary since outcome studies have seldom been conducted in true inception cohorts and many of the follow-up studies were carried out decades ago. Furthermore, the characteristics of the Canadian health system can decrease the referral bias that may have occurred in some of the previously published reports.

This is a study of medium duration (6 to 7 years). This length of follow-up was chosen for two main reasons: a) most published studies are of short duration (≤ 3 years) and b) It has been suggested that the period between 5 and 10 years after onset is the most crucial in determining long-term prognosis (225, 232).

CHAPTER 4

PATIENTS AND METHODS

1.DESIGN OF THE STUDY

The study protocol was based on a retrospective cohort design with a follow-up at 6.5 years. An inception cohort of RA patients with an onset of disease in 1985 was identified retrospectively. Patients then were assessed during the period from August 1991 through June 1992.

2.SELECTION OF THE STUDY COHORT

In order to accomplish the objectives of the study, the first step was to assemble an inception cohort of patients with RA, with an onset of disease in 1985 and residing in metropolitan Edmonton at the time of onset. To avoid inclusion of patients with erroneous diagnoses, it was decided that only patients with a diagnosis of RA by a rheumatologist would be considered for inclusion in the cohort. It is possible that some of the patients with RA may never consult a rheumatologist. Yet, it was considered that this approach was better than including patients followed solely by a family or general practitioner. Since the selection of the cohort would be based in some cases on a past diagnosis of RA (for those patients lost to follow-up or in remission), it was thought that diagnosis certainty would be difficult to achieve unless documented and confirmed by a specialist. The proportion of patients with RA never seen by a rheumatologist is unknown but was thought to be small, given the universal health care system in place in the province of Alberta which allows for equitable access to the majority of health services including rheumatology consultations. Nine rheumatologists had a medical practice in the city of Edmonton at the beginning of the study (July 1991). Of these, 5 were in practice in 1985 and the other 4 started their practices in subsequent years (1986, 1988, 1989, 1990 respectively). Another rheumatologist had been practicing in

Edmonton before 1985, but retired in 1984. All rheumatologists agreed to participate in the study by allowing the review of their patients' records and medical charts.

The selection of the 1985 inception cohort was conducted in three steps:

1. Initial selection of potential cases from rheumatologists' records
2. Selection of patients complying with specific criteria after review of medical charts
3. Definite inclusion in the study cohort after contacting the patients

2.1 INITIAL SELECTION OF POTENTIAL CASES

Medical records of all patients with a diagnosis of RA, seen for the first time by any of the rheumatologists in Edmonton from January 1 1985 through June 30 1991 were reviewed in order to select potential cases for the cohort. At the time of the study, none of the rheumatologists had an updated computerized database of patients including diagnosis. Each rheumatology practice had its own manual filing procedure. For this reason the selection of patient records had to be performed manually. Thus, different methods were used for different filing systems in order to facilitate the selection of only those patients with a diagnosis of RA:

1. Four rheumatologists had their practices at the University of Alberta Hospital (Rheumatic Disease Unit). For billing purposes, all patients seen at outpatient clinics are recorded in log books which include the name and diagnosis of the patient. A patient identification card also is completed at this time including the patient's name, physician's name, diagnosis and date

of consultation. This card also is completed for all other hospital patients seen in consultation. All log books and patient cards were reviewed. Patients with a diagnosis of RA seen between January 1 1985 and June 30 1991 and residing in metropolitan Edmonton were selected for further review of their medical records.

2. Two rheumatologists used ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) codes for diagnosis *(121)*. Code 714 (Rheumatoid arthritis and related arthropathies) was used to select patients for the study. Billing log books were used in one of the rheumatologists' offices and patient identification cards including an ICD code diagnosis in the other. All patients with a 714 ICD code, seen for the first time between January 1 1985 and June 30 1991 and residing in metropolitan Edmonton were further selected for chart review.

3. The remaining 3 rheumatologists did not have patient identification cards including diagnosis. In these offices all medical charts were reviewed.

2.2 REVIEW OF MEDICAL CHARTS

All the medical charts selected following the procedures just described were reviewed by a rheumatologist in order to select potential patients for the 1985 inception cohort. The following inclusion criteria were used at this point:

1. Diagnosis of RA as stated by the rheumatologist in the medical chart.

2. Onset of disease in 1985: onset was defined as the initiation of arthritis symptoms, in particular joint swelling, as stated in the medical charts. In

some cases, the year of onset was not clearly recorded: these patients were provisionally included in the cohort at this stage until more information could be obtained from other sources.

3. Minimum age of 16 years at onset of RA.

4. Residence in the metropolitan Edmonton area at the time of onset. The following communities were included: Edmonton, St Albert, Stony Plain, Spruce Grove, Sherwood Park and Fort Saskatchewan. This selection had already been performed at previous steps in those cases where the information was available from patient identification cards.

2.3 DEFINITE INCLUSION IN THE COHORT

All patients selected after review of their medical charts were initially contacted by mail. A form letter was mailed to them explaining the purpose of the study and inviting them to participate (Appendix 1). A second identical letter was sent to those patients who did not respond to the first one. If no response was obtained, patients were contacted by telephone and invited to participate in the study. When a patient had moved or had been lost to follow-up by the rheumatologist, the family physicians listed in the rheumatologist's chart were contacted to obtain further information on the whereabouts and medical status of the patient. Patients with a revised diagnosis not including RA or with a year of onset other than 1985 were excluded from the study cohort at this point.

Potential cases that agreed to participate in the study were assessed for inclusion after a clinical examination. At this stage, patients were included in the 1985 inception cohort if they satisfied all of the following criteria:

1. Diagnosis of RA by a rheumatologist.

2. Diagnosis of RA according to the 1987 American Rheumatism Association (ARA) criteria (Appendix 2) *(11)*.

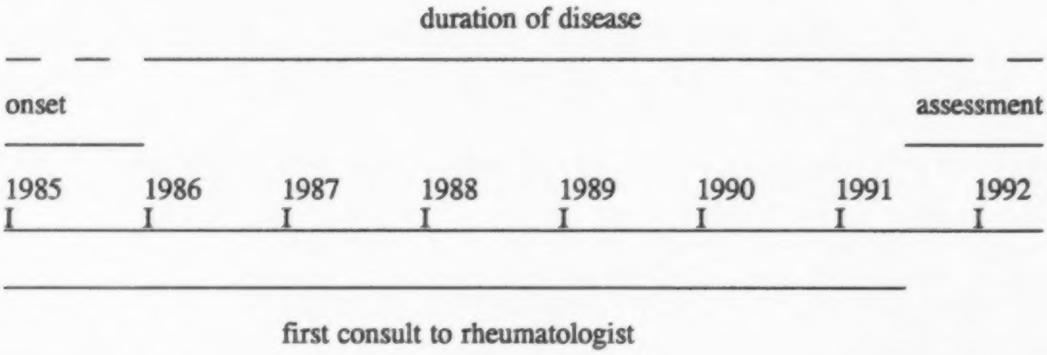
3. Onset of RA symptoms in 1985 as confirmed by the patient or medical chart.

4. Minimum age of 16 years at onset.

5. Residence in metropolitan Edmonton (i.e. the City of Edmonton and surrounding communities, as specified above) at the onset of disease.

3. TEMPORAL SEQUENCE OF THE STUDY

The following diagram illustrates the temporal sequence of the study:


duration of disease
onset
assessment
1985
1986
1987
1988
1989
1990
1991
1992
first consult to rheumatologist

All patients with an onset of disease in 1985 who consulted a rheumatologist at any time from January 1985 to June 30 1991 were considered for inclusion in the inception cohort and contacted between August 1991 and June 1992; those complying with the required criteria and willing to participate in the study were assessed at that point.

4. VALIDATION OF THE INCEPTION COHORT

As previously discussed, a major requirement in outcome studies is the selection of a study sample representative of all newly diagnosed cases of RA to avoid the potential confounding effect of traits present in the study cases that differ from those of non-participants. To confirm that the selected sample was a true inception cohort the following steps were followed:

1. A sample of physicians was sent a questionnaire (Appendix 3) with the purpose of establishing the frequency with which patients with RA were referred for consultation to a rheumatologist. Since the proportion of patients that never saw a rheumatologist was unknown, this survey provided an approximation of referral rates. One hundred and sixty physicians were randomly selected from all physicians listed in the 1991 medical directory of the Alberta College of Physicians and Surgeons complying with the following criteria: a) listed address (generally corresponding to the practice address) in metropolitan Edmonton, b) specialty not listed (includes general practitioners) or listed as family practitioners (Fellows of the Canadian College of Family Physicians) or Internal Medicine specialists. The purpose of this survey was to confirm the hypothesis that most patients with RA seen by general and family practitioners and internists were seen at some point in time by a rheumatologist, and could then be captured by our selection procedures. There may still be a proportion of patients with RA who never seek medical services. Yet, these patients can only be identified through population surveys. Diagnosis certainty is particularly

difficult in these cases, since follow-up studies have shown that many of the individuals selected through population surveys do not appear to have RA when properly ascertained.

2. Demographic characteristics of participants and non-participants were compared to investigate any possible differences that could confound the results.
3. A single advertisement was placed in the Edmonton Chapter of the Arthritis Society newsletter, inviting patients with RA and an onset of disease in 1985, to contact the Rheumatic Disease Unit at the University of Alberta.

5. PROCEDURES AND INSTRUMENTS

All patients contacted were invited to come to the University of Alberta Hospital for a personal interview and a medical examination. Those patients who were unable or unwilling to come were offered a home visit as an alternative.

The following procedures and instruments were used in the study:

5.1 EXTRACTION OF MEDICAL CHART INFORMATION

Medical information from the rheumatologists charts was extracted and coded by a rheumatologist using structured forms. Information was obtained on numbers of visits, general medical status, laboratory and radiological procedures, medication and other forms of therapy (Appendix 4).

5.2 PERSONAL INTERVIEW

The personal interview included details of the medical history and information related to the variables under study, and was conducted using a structured questionnaire (Appendix 5) based on characteristics of the disease, utilization of different therapies and general health status.

5.3 PHYSICAL EXAMINATION

The physical examination was conducted in all cases by the same investigator and included:

a. ***Number of tender and/or painful joints.*** The following joints and joint groups were examined for tenderness and/or pain on passive motion: cervical spine, shoulders, elbows, wrists, MCP joints, PIP joints, hips, knees, ankles and MTP joints. The range of possible scores for this measure is 0 to 35.

b. ***Joint pain and tenderness index.*** This index was based on the evaluation of the same joints and joint groups as above but each of these was weighted according to the severity of the pain and tenderness. The weights were applied as follows:

0 - no pain on motion or tenderness

1 - minimal (on questioning)

2 - moderate (spontaneous response)

3 - severe (withdrawal)

The range of possible scores for this measure is 0 to 105.

c. ***Number of swollen joints.*** The following joints were included: elbows, wrists, MCP joints, PIP joints, knees and ankles. The range of possible scores for this measure is 0 to 28.

d. ***Articular index or swollen joints index.*** The joints evaluated in this score were the same as those included in the number of swollen joints. Each joint was weighted according to the severity of the swelling. Weights were applied as follows:

0 - no swelling

1 - mild (synovial thickening without loss of bone contour)

2 - moderate (loss of bone contour)

3 - severe (bulging synovial proliferation with cystic characteristics)

The range of possible scores for this measure is 0 to 84.

e. ***Number of joints areas with restricted range of motion (ROM).*** This measure was based on the crude evaluation by the investigator of the range of motion. Different joints and joint groups were evaluated for restriction in the range of motion, including: cervical spine, shoulders, elbows, wrists, hands, hips, knees and ankles. Restriction in the range of motion of the hands was evaluated as ability to complete a fist and was given a weight of 5 for each hand. The range of possible scores for this measure is 0 to 23.

f. ***ROM index.*** This index was based on the same joints and joint groups described above, using the same weights for the hands. Additional weights were incorporated according to the degree of restriction in the range of motion as follows:

0 - normal range of motion

1 - mild to moderate restriction in the range of motion (range ≥ 50% of the normal range)

2 - moderate to severe restriction in the range of motion (range < 50% of the normal range)

This index was based on a crude approximation from the investigator's examination and not on goniometric measurements.

The range of scores for this measure is 0 to 46.

5.4 SELF-RESPONSE QUESTIONNAIRE.

This questionnaire (Appendix 6) included the modified Health Assessment Questionnaire (MHAQ-ADL) *(195)* for activities of daily living, as well as information on social variables. The MHAQ is a validated and reliable instrument designed to assess the functional capacity of patients with arthritis. It is based on 8 common functional activities which are rated by the patient from 0 to 3 according to the degree of difficulty with which the task is performed (0=no difficulty, 3=unable to do). The score is obtained by averaging the 8 activities and has a range of 0 to 3.

5.5 RADIOGRAPHS OF THE HAND

A current standard postero-anterior radiograph of the hand was taken at the time of the assessment. The X-rays were simultaneously evaluated by two rheumatologists, blinded to the patients' names and clinical characteristics. A score described by Fries *(87)*, adapted from the original Sharp score *(229, 230)* was used. This score combines erosive damage and joint space narrowing. Radiological damage was graded as follows:

a. Erosions. The following areas were graded for erosions: 2nd to 4th proximal interphalangeal joints, 2nd to 4th metacarpophalangeal joints and ulnar styloid. Weights for each joint were applied as follows:

0 - no erosions

1 - single marginal erosion

2 - marginal erosions on both articular surfaces

3 - extensive erosive process involving less than 50% of the articulating surface

4 - extensive erosive process involving more than 50% of the articulating surface

b. Joint space narrowing. The following joints were evaluated separately for each hand: worst PIP, worst MCP and radiocarpal. Weights were applied as follows:

0 - no joint space narrowing

1 - focal

2 - narrowing of < 50% of original joint space

3 - narrowing of ≥ 50% of original joint space

4 - Ankylosis

The final radiological score was calculated as the sum of the erosion and joint space narrowing scores. The range of scores for this measure is 0 to 96.

Test re-test reliability for radiograph scores

The first 30 radiographs were read and scored on two separate occasions, two weeks apart, following the procedures described above. The purpose of this process was to establish the degree of reliability in the scoring. The Pearson's correlations between the two readings were as follows:

a. Erosion score	$r=0.96$	$p=0.002$
b. Joint space narrowing score	$r=0.94$	$p=0.002$
c. Total radiological scores	$r=0.96$	$p=0.002$
d. Individual joint readings	$r=0.88$	$p=0.002$

5.6 LABORATORY TESTS.

The following laboratory tests were performed:

a. Complete blood count and Westergren sedimentation rate

b. Rheumatoid factors.

Rheumatoid factor titres were measured with a standard commercial latex agglutination assay (Baxter Diagnostics Inc). A titre of 1/40 or more was considered positive

c. Antinuclear antibodies (ANA).

Antinuclear antibodies titres were measured using commercial HEp2 cells (Kallestad) as antigen and a standard indirect immunofluorescence technique. A titre of 1/40 or more was considered positive, based on previous results standardizing this test.

d. Extractable nuclear antigen profile (ENA).

All sera were tested undiluted. If positive, titrated sera were tested against Sm, RNP, SSA and SSB reference sera using Ouchterlony double diffusion assays.

e. Anti-DNA antibodies.

Sera of patients with positive ANA were tested for anti-DNA antibodies. Sera were incubated with Tritium-labelled DNA. Preparations were then filtered through Millipore filters (0.45 um). Results were expressed as percentage of total counts with $\leq 10\%$ being considered normal.

5.7 HLA DR4 TYPING.

HLA DR4 typing was performed in 87 patients. Two hundred ng of genomic DNA from patients was amplified through polymerase chain reaction (PCR) techniques using HLA DR4 group-specific oligonucleotide primers. Reagents included 0.2μm oligonucleotide, 100μm nucleotides, 50 mM KCl, 100 nM Tris at pH 8.3 and 2 units of Taq polymerase. Amplification was performed at 94°C for 30s, 57°C for 30s, 72° for 30s, for 30 cycles. Positive control genomic DNA included a DR4 cell line. Negative control genomic DNA included DR4 negative cell lines. A water control was included with each PCR amplification.

Allelic variants for hypervariable regions were not determined at this time.

6. STUDY VARIABLES

Variables used in the study were numerically coded. Variable names, descriptions and codes are included in Appendix 7.

Several of the variables in the questionnaires and codebook were not incorporated at this time but were recorded as baseline measurements for future follow-up studies of the cohort.

7. CLINICAL STATUS AND OUTCOME MEASURES

Three different types of indices were used to assess the current clinical status and outcome of patients.

a. Indices of disease activity.

- number of swollen joints and swollen joint index

- number of painful/tender joints and joint pain and tenderness index

- duration of morning stiffness

- intensity of pain (VAS)

- Blood hemoglobin concentration

- ESR

b. Radiological scores - The radiological score was used as a measure of articular damage

c. MHAQ-ADL - The MHAQ-ADL was used as a measure of physical functional status.

Indices of disease activity can often be considered as outcome measures, particularly in clinical trials. Yet, because of their variability during flares and remissions, they are probably better defined as measures of current clinical status. However, to facilitate interpretation, the term 'outcome measures' will be used throughout the text to include all variables measuring clinical status: those related to disease activity as well as those more effectively reflectingt long-term outcome (radiological damage and functional status).

8. STATISTICAL METHODS

8.1 BIVARIATE ANALYSES

The initial exploratory analyses were conducted using the following statistical tests *(9)*:

a. Chi-square tests to determine differences between proportions. A Fisher's exact test was used in 2 by 2 tables with one or more cell counts under 5.

b. *t*-tests to determine the differences in means between 2 groups. An *F* test was used to test for the equality of the variances. If the *F* test was significant ($\leq$ 0.05) a t-test based on separate variance estimates was conducted. Otherwise, a pooled variance t-test was used.

c. One way analysis of variance to determine the differences in means between 3 or more groups.

d. Pearson's correlation coefficients

e. Kaplan-Meier survival methods were used to study probability of discontinuation of different drug regimes *(96)*

8.2 MULTIVARIATE ANALYSES

The following statistical methods were used:

A. Multiple Linear Regression

Multiple linear regression was used to determine the adjusted associations of the different independent variables of interest with the dependent variables (outcome measures). The general model for multiple linear regression can be expressed as follows *(10)*:

$$Y = \alpha + ß_1X_1 + ß_2X_2 + \ldots + ß_KX_K + e$$

where X_K is the value of the Kth independent variable for each individual, ß the unknown population coefficients, and e the independent random errors.

Coefficients were determined through ordinary least squares estimation. Different models were examined following two methods:

a) stepwise regression, where independent variables were examined at each step for entry or removal according to the level of statistical significance. The purpose of using this method was to identify only those variables that were significantly associated with outcome.

b) forced entry, where all the independent variables considered to be relevant were entered in the model whether the coefficients were statistically significant or not. The purpose of this technique was to obtain estimates controlling for variables that were thought to have a small effect that did not reach statistical significance. Adjusting for age and sex, for example, is done often regardless of the statistical significance.

Only those interactions thought to be relevant and in agreement with the proposed theoretical framework were tested.

B. Multiple Logistic Regression.

Logistic regression techniques were used for the following purposes:

a) to evaluate dependent variables with a skewed distribution as dichotomous variables

b) to obtain odds ratios, which can be easily interpreted in terms of risks, by categorizing the variables according to clinically meaningful cut points

The general form for multiple logistic regression models can be expressed as *(26)*:

$$\ln \left[\frac{Y}{1 - Y} \right] = \alpha + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k + e$$

For dichotomous dependent variables (e.g. cases and controls), Y is the probability of one of the binary outcomes (e.g. disease) and Y/1-Y is the odds of Y. If the independent variable is binary, the coefficient ß is the logarithm of the odds ratio for that variable in relation to the outcome of interest.

Outcome variables were dichotomized for these models using the median as the cut point. Continuous independent variables also were dichotomized according to their distribution in the sample. Odds ratios were obtained by maximum likelihood estimation.

Again, models were examined following two different methods:

a) backward variable elimination, where all variables were entered and removed one at a time based on the probability value

b) forced entry, where variables thought to be relevant were kept in the model, regardless their level of statistical significance.

Interactions were tested only when supported by the theoretical framework.

c. *Structural equation modelling*

Linear structural equations (LISREL) analysis was used to study direct and indirect associations of the various variables with outcome. LISREL modelling assumes a causal structure among a set of latent variables, with the observed variables as indicators of these latent concepts *(109, 151)*. These methods are particularly useful when the observed variables contain measurement errors, when there is interdependence or simultaneous causation, and when important explanatory variables cannot be measured (omitted variables). This is of particular relevance to the outcome of RA where a variety of factors may have indirect effects and the explanatory power of variables that can be observed is low, with causal factors still unrecognized.

Models tested with LISREL were based on the current knowledge of determinants of outcome in RA, plus the results from the initial linear regression models. Coefficients for the different LISREL models were obtained from maximum likelihood estimates.

Initial data manipulation and multiple regression analyses were conducted using the Statistical Package for the Social Sciences for the IBM PC (SPSS/PC+) *(246)*. Logistic regression models were tested using EGRET *(68)*, a logistic regression software package for microcomputers *(68)*. LISREL models were obtained using the LISREL program *(151)* available in SPSS-X through the University of Alberta mainframe system (Michigan Terminal Systems - MTS).

9. STATISTICAL POWER

The statistical power of this sample was estimated as follows *(49)*:

- differences between 2 means (*t*-test): for a two-tailed level of significance α=0.05, and assuming equal *n*s in both groups, the statistical power 1-ß to detect a difference between groups equivalent to 0.5 of the standard deviation σ was estimated to be 80%

- differences between 2 proportions (chi-square test): for a two-tailed level of significance α=0.05, assuming equal *n*s in both groups, the statistical power 1-ß to detect a difference of 0.25 (when the proportion of the trait under study in one of the groups is $p=0.50$) was estimated to be 80%.

- multiple regression procedures: for a level of significance $\alpha=0.05$, in models with 8 independent variables, the statistical power $1-\beta$ to detect a multiple correlation coefficient $R=0.36$ was estimated to be 85%.

These effects can be considered medium-size, as defined by Cohen (49).

10. ETHICS APPROVAL

Ethics approval for this project was obtained from the Ethics Review Committee for Human Experimentation of the Faculty of Medicine at the University of Alberta. Signed informed consent forms were obtained from all participants.

CHAPTER 5

RESULTS 1

SELECTION OF THE 1985 INCEPTION COHORT

1. INITIAL SELECTION OF THE 1985 COHORT

Nine rheumatologists were practicing in Edmonton at any time between January 1 1985 and June 30 1991; five of them had been in practice before 1985 and the rest started their practices at various times thereafter. All 9 rheumatologists were affiliated to acute care hospitals and had hospital privileges. After completing the first step in the selection of possible cases for the cohort, more than 3,000 charts were selected for review. All of these patients were 16 years or older in 1985 and lived in metropolitan Edmonton. Of these, 2,101 had a confirmed diagnosis of RA by the rheumatologist stated in the chart. After review of the medical records, all RA patients were classified into the following categories according to year of onset:

1. Definite onset in 1985 - onset in 1985 clearly stated in the chart.
2. Probable onset in 1985 - onset not clearly stated by month or year but approximation close to 1985 (e.g. "history of RA for 3 years" recorded in a consult in 1988).
3. Year of onset unknown - onset not stated in the chart
4. Onset before 1985
5. Onset after 1985

Table 5.1 shows the distribution of patients into these categories after chart review. The majority of patients had developed RA either before or after 1985. One hundred and twenty nine (6%) had a definite onset of RA in 1985, and in 83 (4%) the date of start was probably 1985. In 21 cases (1%) the date of onset was not stated. All 233 patients in groups 1 to 3 (definite or probable onset in 1985 or unknown onset) were selected for potential inclusion in the inception cohort pending further assessment.

2. FINAL SELECTION OF THE 1985 INCEPTION COHORT

All 233 patients selected for the cohort were initially contacted by mail, as described in the methods section. If no response was obtained, they were then contacted by telephone. In those cases where a direct contact was not achieved, efforts were made to obtain information on the whereabouts and medical condition of the patients from the family physicians and relatives. One hundred and forty-four patients (62%) were seen. Thirty (13%) were contacted by telephone but were not seen because they either refused to participate or did not qualify for the study. In 38 (16%) additional information was obtained from a third party. In 21 patients (9%) no additional information could be obtained and patient status was unknown.

Table 5.2 shows the final status in relation to inclusion in the cohort according to the type of information obtained. Of the 144 patients assessed, 128 complied with the inclusion criteria and were included in the cohort. Overall, out of the 233 patients, 13 were deceased, and 49 did not comply with the cohort criteria. Of these 49 patients, 35 had an onset of disease before or after 1985; the other 14 patients had a final diagnosis other than RA (e.g. psoriatic arthritis or osteoarthritis) or had a form of arthritis that did not satisfy the ARA criteria. Eleven patients refused to participate, and 32 were lost to follow-up (11 had moved out of town and no information could be obtained for the rest). No effort was made to follow-up those patients who moved out of town.

Table 5.3 shows the final status of patients according to onset as recorded from the medical charts. All assessed patients with an unknown date of onset from the chart review had started with RA either before or after 1985. Only 1 patient in this group was lost to follow-up. As expected, some of the patients in whom onset in 1985 according to their medical records was probable but not definite had started with their disease in a different year. In contrast, only 1 of the patients with a definite onset in 1985 according to the information in the rheumatologist's chart was later found to have developed RA after this date.

Forty-nine patients were not eligible for the cohort and 13 had died, leaving 171 patients who could potentially be part of the inception cohort. Of these, 128 were assessed which gives a participation rate of 75%. This rate was calculated assuming that all 171 patients had RA and that all had a 1985 onset. Yet, of the 212 patients on whom some information had been obtained (Table 5.2, 144 seen, 30 telephoned, 38 with information from a 3rd party) 62 (29.2%) did not comply with the inclusion criteria or were deceased. This suggests that some of the patients that were lost to follow-up, may not have been part of the inception cohort or may have been deceased, and the "true" participation rate in relation to the potential "true" cohort participants is in all probability higher than 75%. Assuming the same rate of misclassification the participation rate is 81%.

As mentioned in the methods section, an advertisement was placed in the Edmonton Chapter of the Arthritis Society newsletter, inviting all patients with RA and an onset of disease in 1985 to contact the Rheumatic Disease Unit at the University of Alberta. This newsletter is received by all individuals with arthritis who are members of the Edmonton Chapter. The only patient who contacted the Unit in relation to the advertisement had an earlier onset of disease and for that reason, was not suitable for inclusion in the inception cohort.

3. COMPARISONS OF PARTICIPANTS WITH NON-PARTICIPANTS

Forty-three patients were considered non-participants: 11 refused to participate, 11 had moved out of town and 21 were lost to follow-up. General characteristics of these patients are shown in Table 5.4. No significant differences were observed between participants and grouped non-participants for the following variables: age, sex, residence in the city of Edmonton in 1985 (as compared to surrounding communities), and year first seen by a rheumatologist. When non-participants were subgrouped into those who had refused to participate, those who moved and those who were lost to follow-up, patients that had moved to another city were younger than those in the cohort. However, as stated above, when all non-participants were considered together, the difference in mean age was not statistically significant.

4. RESULTS OF THE PHYSICIAN SURVEY

A questionnaire (Appendix 3) was sent to the 160 randomly selected physicians. Three of the letters were returned unopened because the physicians had moved. Of the remaining 157 questionnaires, 104 (66.2%) were returned.

Thirty-seven physicians were general practitioners, 41 family physicians, 8 specialists in internal medicine, 5 had retired and 11 had other specialties or were still in training. Thus, altogether, 86 physicians were practicing in the areas of interest in relation to this study (general, family and internal medicine practices). Sixty were male (70%) and 25 female (one physician did not specify gender).

The frequency with which these physicians reported seeing patients with RA was as follows:

- Rarely	18 (21%)
- Sometimes	58 (67%)
- Often	10 (12%)

In the questionnaire, it was asked how often first-time patients with RA were referred to a rheumatologist for a consult and how often their patients with RA were followed by a rheumatologist on a yearly basis. Results are shown in Table 5.5. Sixty-three percent of the physicians referred new patients with RA 90% or more of the time and only 6% referred less than 50% of the new RA patients. The frequency of yearly follow-up was lower: less than a third of the physicians stated that 90% or more of their patients with RA were seen yearly by a rheumatologist. When results were averaged by taking the mid-point of the intervals (95 for 90% or more, 80 for 70 to 90%, etc) an estimated 83% of the new RA patients seeing a general physician (or internist) was referred for consultation to a rheumatologist. Using the same method, it was estimated that 70% would be followed yearly by a rheumatologist. If the averages were calculated using the lower boundaries of the intervals (e.g. less than 50% as 0), 75% of the new RA patients seen by these practitioners would be seen by a rheumatologist and 60% would be followed once a year.

TABLE 5.1. Distribution of patients with RA according to onset, after review of the medical charts

ONSET of RA	**N**	
1. Definite onset in 1985	129	(6%)
2. Probable onset in 1985	83	(4%)
3. Onset unknown	21	(1%)
4. Onset before 1985	1177	(56%)
5. Onset after 1985	691	(33%)
TOTAL	2101	(100%)

TABLE 5.2. Patient status in relation to the inception cohort according to source of information (patients selected after chart review)

	SEEN	PHONED	INFORMATION 3RD PARTY	UNKNOWN STATUS	TOTAL
In 1985 cohort	128	-	-	-	128 (54.9%)
Deceased	-	-	13	-	13 (5.6%)
Refused	-	11	-	-	11 (4.7%)
Moved out of town	-	-	11	-	11 (4.7%)
Unknown status	-	-	-	21	21 (9.0%)
Onset before 1985	8	9	6	-	23 (9.9%)
Onset after 1985	1	5	6	-	12 (5.2%)
Not RA	7	5	2	-	14 (6.0%)
TOTAL	144(62%)	30(13%)	38(16%)	21 (9%)	233 (100%)

TABLE 5.3 Patient status in relation to the inception cohort according to onset status in medical chart (definite onset in 1985, probable onset in 1985, unknown onset)

	DEFINITE	PROBABLE	UNKNOWN	TOTAL
In 1985 cohort	84 (65.1%)	44 (53.0%)	-	128(54.9%)
Deceased	9 (7.0%)	4 (4.8%)	-	13(5.6%)
Refused	9 (7.0%)	2 (2.4%)	-	11(4.7%)
Moved out of town	8 (6.2%)	3 (3.6%)	-	11(4.7%)
Unknown status	11 (8.5%)	9 (10.8%)	1 (4.8%)	21(9.0%)
Onset before 1985	-	6 (7.2%)	17 (81.0%)	23(9.9%)
Onset after 1985	1 (0.8%)	8 (9.6%)	3 (14.3%)	12(5.2%)
Not RA	7 (5.4%)	7 (8.4%)	-	14 (6.0%)
TOTAL	129 (100%)	83 (100%)	21 (100%)	233 (100%)

TABLE 5.4 Characteristics of patients in the cohort vs non-participants

	PATIENTS IN COHORT (n=128)	NON-PARTICIPANTS			
		REFUSED (n=11)	MOVED (n=21)	UNKNOWN (n=23)	TOTAL NON-PARTICIPANTS (n=53)
Age, yrs mean (SD)	58.3 (13.6)*	60.6 (15.4)	45.1 (20.4)*	54.3 (16.3)	53.6 (17.7)
Females, n	90 (70%)	9 (82%)	9 (82%)	15 (71%)	33 (77%)
Residence in City of Edmonton, n	110 (86%)	11 (100%)	8 (73%)	18 (86%)	37 (86%)
Year 1st seen by a rheumatologist, n					
1985-86	96 (75%)	9 (82%)	9 (82%)	14 (67%)	32 (74%)
1987-88	23 (18%)	1 (9%)	1 (9%)	3 (14%)	5 (12%)
1989-91	9 (7%)	1 (9%)	1 (9%)	4 (19%)	6 (14%)

Continuous variables as mean (SD)
* statistically significant

TABLE 5.5 Results of the physician survey. Percentage of patients seen by rheumatologists

	PHYSICIANS' RESPONSES	
% PTS SEEN BY RHEUMATOLOGIST	**FIRST-TIME REFERRAL**	**YEARLY FOLLOW-UP**
>90%	54 (63%)	27 (31%)
70-90%	14 (16%)	22 (26%)
50-70%	13 (15%)	23 (27%)
<50%	5 (6%)	14 (16%)
Total	86(100%)	86(100%)

CHAPTER 6

RESULTS 2

CHARACTERISTICS OF THE 1985 COHORT

OVERALL OUTCOME

1. GENERAL CHARACTERISTICS OF THE COHORT

1.1 DEMOGRAPHIC CHARACTERISTICS

One hundred and twenty-eight patients were included in the cohort. Demographic characteristics are shown in Table 6.1. Seventy percent were female. The mean age at onset was 51.7 years. Approximately 86% of the patients lived in the City of Edmonton in 1985 and the rest in the other surrounding communities included in the study. The majority of patients (93.8%) were of Caucasian origin.

1.2 DIAGNOSIS OF RA ACCORDING TO THE ARA CRITERIA

The presence of ARA diagnostic criteria (Appendix 2) was ascertained as follows:

1. Criterion 1 (morning stiffness) was considered positive if stated in the medical chart or described by patient.
2. Criteria 2, 3, 4 and 5 (joint swelling and subcutaneous nodules) were considered positive, only if present at the time of ascertainment and evident by physical examination or if stated by the rheumatologist in the medical chart.
3. Criteria 6 and 7 (positive RF and radiological changes) were considered present if positive at the time of ascertainment or in previous tests taken at any time during the course of the disease.

Overall, 27 patients (21%) were positive for 7 criteria, 34 (27%) for 6, 45 (35%) for 5 and 21 (16%) for 4. An additional patient was positive for 3 criteria only, but it was decided to include him because he had an amputation of his right upper extremity and the criterion of symmetrical swelling could not be evaluated.

Patients were categorized for each criterion as: a) negative, b) currently positive and c) previously positive and currently negative (Table 6.2). Over 99% of the patients had been positive at any time for criteria 2, 3 and 4 which relate to the clinical characteristics of swelling. Fifty-nine percent of the patients could be considered seropositive. The presence of rheumatoid nodules (criterion 5) was the least frequently positive criterion, observed in 33.6% of the patients. Criteria 1 to 4 were more likely to change in a given patient. Approximately a third of those patients who had been positive for criterion 3 (swelling of PIP, MCP or wrists) were negative for this criterion at the time of ascertainment. Approximately half of those positive for criterion 1 (morning stiffness), criterion 2 (swelling of 3 joint areas) and criterion 4 (symmetrical swelling) were negative at the time of assessment. The 2 patients with previous x-ray changes and normal x-rays at ascertainment had juxta-articular osteoporosis but no erosions in the previous radiological assessment. The changes in rheumatoid factor could not be evaluated with precision: although some patients with negative RF at the time of assessment had previously been positive, the exact proportion is unknown since there were no previous RF recorded in the medical charts of 19 of the 128 patients.

1.3 CLINICAL CHARACTERISTICS

A. Onset

Onset of disease was categorized as gradual, acute or palindromic. Gradual onset was defined as an insiduous start with symptoms developing over weeks or months. Acute onset was defined as development of symptoms within 2 days. Patients with palindromic rheumatism were considered to develop RA when their attacks became chronic with a duration of at least 6 weeks, and with compliance of the ARA criteria for the diagnosis of RA.

Frequencies of type of onset were as follows:

- Gradual	94 (73.4%)
- Acute	20 (15.6%)
- Palindromic	14 (10.9%)

B. Course

The course of RA was categorized into chronic, remittive, palindromic and single flare, defined as:

- *Chronic* - continuous arthritis with no remissions

- *Remittive* - at least one remission for a minimum of 3 months. Patients with a single flare who continued in remission after several years were considered to have a 'single flare' course (see below).

- *Palindromic* - Characteristic attacks of palindromic rheumatism with at least one episode of arthritis of a minimum of 6 weeks duration to comply with the ARA criteria.

- *Single flare* - Initial flare lasting 3 years or less, followed by sustained remission up to the time of ascertainment.

Patients were categorized according to course as follows:

- Chronic	52 (40.6%)
- Remittive	50 (39.1%)
- Palindromic	4 (3.1%)
- Single flare	22 (17.2%)

Duration of disease was rounded to the closest number of years (6 or 7): 62 patients had a disease duration of 6 years and 66 patients, 7 years. Mean duration of disease was 6.5 years ± 0.5.

C. Articular involvement

The prevalence of articular swelling in the different joint areas at the time of the assessment was:

- MCP joints	69 patients	(53.9%)
- PIP joints	49 patients	(38.3%)
- Wrists	36 patients	(28.1%)
- Knees	31 patients	(24.2%)
- Elbows	26 patients	(20.3%)
- Ankles	7 patients	(5.5%)

Limited range of articular motion at the time of assessment was observed as follows for the different joint areas:

- Cervical spine	34 patients	(26.6%)
- Shoulders	53 patients	(41.4%)
- Elbows	24 patients	(18.7%)

- Wrists	77 patients	(60.2%)
- Fists	44 patients	(34.4%)
- Hips	3 patients	(2.3%)
- Knees	9 patients	(7.0%)
- Ankles	6 patients	(4.7%)

Thirty five patients (27.3%) had hand deformities: 28 had MCP subluxation (21.9%), 15 had ulnar deviation (11.7%) and 9 (7%) one or more finger deformities such as 'swan-neck' or 'boutonniere'.

1.4 DISEASE ACTIVITY AT THE TIME OF THE ASSESSMENT

Disease activity measures included duration of morning stiffness, pain assessment using a 10 cm visual analogue scale (VAS), joint counts and indices, blood hemoglobin and ESR. The number of joints with limited ROM was included with the other joint counts to facilitate comparisons, although it does not truly represent a measure of joint activity alone. Results were as follows [mean, median (SD)].

- Morning stiffness (minutes)	40.4	15.0	(61.9)
- Pain (VAS) (mm)	29.4	27.5	(23.2)
- N° tender joints	3.2	2.0	(3.7)
- Tenderness index	3.7	2.0	(4.2)
- N° swollen joints	4.4	2.5	(5.6)
- Articular index	6.2	3.0	(9.1)
- Limited ROM joints	5.2	3.0	(5.7)
- Limited ROM index	6.3	3.0	(7.3)

- Hemoglobin (g/dl)	13.5	13.6	(1.6)
- ESR (mm Hg)	24.5	21.5	(15.3)

Many of the variables, in particular morning stiffness and the joint indices had distributions skewed to the right. Forty-one patients (32.0%) had no articular swelling, 33 patients (25.8%) had no painful or tender joints and 29 (22.7%) had a normal range of motion as assessed by the crude indices.

1.5 RHEUMATOID FACTORS AND ANTINUCLEAR ANTIBODIES

At the time of the assessment, 61 patients (48%) had positive RF. Overall, 75 patients (59%) had a positive RF at any point in the disease and were considered as seropositive for the statistical analyses.

Antinuclear antibodies using HEp2 cells as a substrate were observed in 78 of the 119 patients tested (65.6%), with a mean titre of 199 (±272 SD). The mean titre for all patients was 130 (±239 SD). The most frequently observed pattern was speckled, in 52 cases (67%).

Antibodies against extractable nuclear antigens were observed in 24 of the 118 (20.3%) patients tested. Of these patients, 2 had positive anti-RNP, 2 positive anti-SSB and 1 anti SSA. The rest of sera could not be identified with any of the antigens tested.

Testing for anti-DNA antibodies was conducted in all patients with positive ANA. Results were borderline for 1 patient and negative for the rest.

1.6 RADIOLOGICAL CHANGES

One hundred and twenty six patients had X-rays of the hands. X-rays were scored following the method previously described. Three scores were obtained: a) joint space narrowing score, b) erosion score and c) total radiological score, which was the sum of a) and b). Results were as follows [mean, median (SD)]:

- Joint space narrowing	2.6	1.0	(3.2)
- Erosions	3.7	2.0	(5.7)
- Total radiological score	6.3	4.0	(8.2)

The distribution of the radiological scores was skewed to the right. Twenty-nine patients (23%) had a radiological score of 0. Thirty-nine patients (31%) had no erosions. Juxta-articular osteoporosis was observed in 28 cases (22%).

1.7 FUNCTIONAL STATUS

Functional status was measured using the ADL portion of the MHAQ instrument. The range of possible scores for this measure is 0 to 3. One hundred and twenty seven patients completed this questionnaire. The distribution of the MHAQ-ADL was skewed to the right. The mean value of the MHAQ score was 0.49 (±0.47) and the median 0.38. Thirty-nine patients (30.7%) had a score of 0, equivalent to normal capacity for the evaluated functions. Seventy-five patients (59.1%) had a score between 0.10 and 1.00 and the rest (10.2%) scored between 1.10 and 2.00. The maximum score reported was 1.88.

1.8 REMISSION

The American Rheumatism Association criteria for remission were applied *(187)*. The criteria are as follows:

1. duration of morning stiffness not exceeding 15 minutes

2. no fatigue

3. no joint pain (by history)

4. no joint tenderness or pain in motion

5. no soft tissue swelling in joints or tendon sheaths

6. ESR (Westergren method) less than 30mm/h for females and 20mm/h for males.

Criterion 2 had not been ascertained at interview in these patients and was therefore not used. Criterion 3 was evaluated with the VAS pain scale.

Only 4 patients complied with all 5 criteria examined. Criteria were then applied consecutively. The order in which the criteria were applied was somewhat arbitrarily chosen, using clinical judgement as to which were the elements best assessing disease activity.

1 - no joint swelling: 41 patients (32%) complied with this criterion

2 - no joint swelling and ESR criterion: 30 patients (23%) complied with these 2 criteria

3 - no joint swelling, ESR criterion and morning stiffness of less than 15 minutes: 20 patients (16%) complied with these 3 criteria

4 - no joint swelling, ESR criterion, morning stiffness criterion and no tender joints: 15 patients (12%) complied with these 4 criteria

5. All of the above and VAS analogue scale of 0: 4 patients (3%) complied with the 5 criteria

2. COURSE OF THE DISEASE AND ASSOCIATIONS WITH OTHER DISEASE CHARACTERISTICS

Table 6.3 shows the distribution of patients according to the various types of disease onset and subsequent course. Forty-three percent of the patients who had a gradual onset developed a chronic course, compared to 35% and 36% of those who had an acute or palindromic onset. This difference was statistically significant when comparing palindromic onset to the other categories grouped together (Fisher's exact test $p<0.001$). Of these, 29% remained in a palindromic course, after having experienced at least one flare of a minimum of 6 weeks duration (required as an inclusion criterion). Two of the patients with palindromic arthritis who experienced a single flare with subsequent remission of all symptoms, including the palindromic attacks, were included in the 'single flare' course group.

Demographic characteristics including gender and age at onset according to course type are shown in Table 6.4. Patients with a remittive and palindromic type of arthritis were younger than those with chronic disease or a single flare. No significant differences were observed for gender.

Selected clinical characteristics, and joint counts, are shown in Table 6.5.

Patients with a chronic course had a statistically significant increase in all joint indices compared to patients in the other 3 groups (Tukey's method, level of significance $\alpha=0.05$). Similarly there was an increase in the presence of rheumatoid nodules and deformities of the hands when compared to the other groups. Table 6.6 shows other outcome measurements in relation to the course of RA. Statistically significant differences were observed for pain, radiological score, MHAQ, ESR and hemoglobin. Although the duration of morning stiffness was longer in the chronic group, it did not achieve statistical significance ($p=0.06$)

The distribution of patients with positive RF, HLA DR4 and ANA according to course of the disease is shown in Table 6.7. No significant differences were observed for any of the 3 variables.

3. BIVARIATE ANALYSIS: ASSOCIATIONS OF OUTCOME MEASURES

The purpose of these analyses was to study the association of selected variables with the different outcome measures. At this point, only bivariate associations were sought as an initial exploratory analysis.

3.1 DEMOGRAPHIC CHARACTERISTICS

Associations of gender with relevant clinical characteristics and outcome measures are shown in Table 6.8. A statistically significant difference was observed for hemoglobin and ESR. This difference disappeared, however, when adjusted for the normal variations between males and females.

To study the effects of age, age at onset was chosen as the variable of interest. Since all patients had a duration of disease between 6 and 7 years, the correlation between age and age at onset was 0.99. It was thought that age at onset would facilitate generalizability in the interpretation of results and comparisons with other series with different duration of disease. Bivariate correlations of age at onset with selected clinical characteristics and outcome parameters were as follows:

- Nº of tender joints	0.07	(p=0.43)
- Tenderness index	0.12	(p=0.12)
- Nº of swollen joints	-0.06	(p=0.47)
- Articular index	-0.07	(p=0.44)
- Nº of limited joints	0.25	(p=0.004)
- ROM index	0.23	(p=0.008)
- MHAQ-ADL	0.28	(p=0.001)
- Radiological score	0.10	(p=0.27)
- RF	-0.03	(p=0.76)
- HLA DR4	0.08	(p=0.46)
- ESR	0.27	(p=0.004)
- Hemoglobin	-0.14	(p=0.11)

Statistically significant positive correlations were observed for age at onset and MHAQ, ROM indices, and ESR.

3.2 TYPE OF ONSET

Patient characteristics and outcome measurements in the 3 onset groups are shown in Table 6.9 and 6.10. No statistically significant differences were observed for any of the variables.

3.3 RHEUMATOID FACTOR

Characteristics of patients and outcome measures according to RF status are shown in Table 6.11. Patients with at least one positive test, present or past, were considered seropositive. Statistically significant differences were observed for the number of swollen joints, articular index, nodules, ESR and positive ANA. All these parameters were increased in seropositive patients. Rheumatoid factors were negative in 10 patients with nodules. Four of these patients did not have a RF test before the study and their previous status is thus, unknown. The other 6 patients had at least 2 negative tests for RF. Antinuclear antibodies were detected in 75% of 71 seropositive patients compared to 50% of 48 seronegative patients tested ($p=0.006$).

3.4 HLA DR4

Eighty-seven patients were HLA typed for the class II DR4 antigen. No significant differences were observed between DR4 positive and DR4 negative individuals (Table 6.12).

3.5 NODULES

Table 6.13 shows the relationship of rheumatoid nodules to other disease characteristics. The presence of nodules was significantly associated with an increase in the swollen and limited joint indices, the presence of hand deformities and the radiological score. In addition, patients with nodules were younger at onset than patients without nodules.

3.6 SOCIOLOGICAL VARIABLES

The associations of selected sociological variables with other factors were also examined. Bivariate correlations between education level and total household income, and disease characteristics are shown in Table 6.14. Education and total household income for 1990 were measured in ordinal scales (1 to 18 for education, 1 to 8 for income, Appendix 7), and treated as continuous.

Education showed a statistically significant negative correlation with age at onset, tenderness index and MHAQ. Total household income showed a statistically significant negative correlation with age at onset, tender joints indices and MHAQ.

A statistically significant positive correlation was observed between education level and total household income ($r=0.45$, two-tailed $p<0.001$).

Disease characteristics were also examined in relation to marital status. For this analysis all married individuals were compared against single (never married), separated, divorced and widowed grouped together. Results are shown in Table 6.15. No significant differences were observed for the different disease characteristics. Education level was similar for married and non-married individuals. A significant difference was observed for total household income, with married patients reporting higher levels.

No significant associations were observed between education, income, marital status and the different types of disease onset and disease course.

4. ASSOCIATIONS AMONG OUTCOME MEASURES

Correlations among the different outcome measures are shown on Table 6.16. Most indices were significantly correlated among themselves. The exception was the radiological score: no significant associations were found between this index and number of tender joints, MHAQ-ADL and ESR. Results were similar when using weighted joint counts (not shown).

Table 6.1. Demographic characteristics of the 1985 inception cohort

Females, n	90	(70.3%)
Age,yrs - mean (SD)	58.3	(13.4)
Age at onset,yrs - mean (SD)	51.7	(13.4)
Residence in 1985, n		
City of Edmonton	110	(85.9%)
Surrounding communities	18	(14.1%)
Ethnic background, n		
Caucasian	120	(93.8%)
Black	1	(0.8%)
Oriental	2	(1.6%)
North-American Indian	2	(1.6%)
East-Indian	3	(2.3%)

Table 6.2. American Rheumatism Association criteria for the diagnosis of RA in the 1985 inception cohort

	N/A	CURRENTLY POSITIVE	PREVIOUSLY POSITIVE *	TOTAL EVER POSITIVE	NEGATIVE
CRITERION 1 Morning stiffness	-	42(32.8%)	68(53.1%)	110(85.9%)	18(14.1%)
CRITERION 2 Swelling 3 joints	-	56(43.8%)	71(55.5%)	127(99.2%)	1(0.8%)
CRITERION 3 Swelling PIP,MCP,wrist	-	82(64.1%)	45(35.2%)	127(99.2%)	1(0.8%)
CRITERION 4 Symmetrical Swelling	1(0.8%)	67(52.8%)	59(46.5%)	126(99.2%)	1(0.8%)
CRITERION 5 Nodules	-	35(27.3%)	8(6.3%)	43(33.6%)	84(66.4%)
CRITERION 6 Rheumatoid factor	1(0.8%)	61(48.0%)	14(11.0%)	75(59.1%)	52(40.9%)
CRITERION 7 X-ray changes	2(1.6%)	95(75.4%)	2(1.6%)	97(77.0%)	29(23.0%)

N/A - not available (missing values)
percentages for positive criteria are calculated in relation to available data
* previously positive and currently negative

TABLE 6.3 Course of RA according to type of onset

	ONSET			
COURSE	**Gradual**	**Acute**	**Palindromic**	**TOTAL**
Chronic	40 (42%)	7 (35%)	5 (36%)	52
Remittive	37 (40%)	10 (50%)	3 (21%)	50
Palindromic	-	-	4 (29%)	4
Single flare	17 (18%)	3 (15%)	2 (14%)	22
TOTAL	94(100%)	20(100%)	14(100%)	128

TABLE 6.4 Demographic characteristics according to course of RA

COURSE	**N**	**Age onset*** mean (SD)	**N° females**** n (%)
Chronic	52	55.5 (11.8)	38 (73%)
Remittive	50	46.9 (12.7)	37 (74%)
Palindromic	4	39.7 (7.2)	4 (57%)
Single flare	22	58.2 (14.3)	11 (58%)
TOTAL	128	51.7 (12.4)	90 (70%)

* F=8.7, p =0.0001
** not statistically significant

TABLE 6.5 Joint indices, rheumatoid nodules, and hand deformities according to course of RA

	DISEASE COURSE				
	Chronic (n=52)	**Remittive** (n=50)	**Palindromic** (n=4)	**Single flare** (n=22)	**p value**
Nº tender joint	4.8 (4.2)	2.8 (3.1)	1.7 (1.3)	0.5 (0.9)	0.0001 *
Tenderness index	5.5 (4.6)	3.2 (3.7)	1.7 (1.3)	0.6 (1.1)	0.0001 *
Nº swollen joints	7.6 (6.1)	3.3 (4.4)	0.5 (1.0)	0.0 (0.0)	0.0001 *
Articular index	11.3 (11.1)	4.1 (6.0)	0.5 (1.0)	0.0 (0.0)	0.0001 *
Nº limited joints	8.5 (6.1)	3.9 (4.7)	0.5 (1.0)	1.3 (2.4)	0.0001 *
ROM index	10.4 (8.0)	4.7 (6.1)	0.5 (1.0)	1.4 (2.6)	0.0001 *
Nodules	24 (46%)	14 (28%)	2 (50%)	3 (13%)	0.03 *
Hand deformities	27 (52%)	6 (12%)	-	2 (9%)	0.0001 *

Continuous variables shown as mean (SD)
*statistically significant

TABLE 6.6 Other outcome measures according to course of RA

	DISEASE COURSE				
	Chronic (n=52)	**Remittive** (n=50)	**Palindromic** (n=4)	**Single flare** (n=22)	**p value**
Pain scale(VAS)	36.7 (19.0)	28.5 (26.7)	22.0 (19.2)	16.5 (17.2)	0.009*
Morning stiffness	57.3 (76.9)	33.4 (52.8)	23.8 (27.5)	19.1 (29.1)	0.06
Xray score	9.9 (10.2)	5.1 (5.9)	0.8 (1.5)	1.7 (1.9)	0.0001*
MHAQ-ADL	0.66 (0.42)	0.40 (0.48)	0.19 (0.30)	0.34 (0.45)	0.004*
ESR	31.2 (16.9)	22.9 (12.4)	6.7 (6.4)	15.0 (9.9)	0.0001*
Hemoglobin	12.9 (1.5)	13.7 (1.7)	14.6 (1.6)	14.4 (1.2)	0.0007*

Continuous variables shown as mean (SD)
* statistically significant

TABLE 6.7 Rheumatoid factors, HLA DR4 and ANA according to course of RA

	Pos RF* (n=127)	**HLA DR4*** (n=87)	**Pos ANA*** (n=119)
Chronic	35 (67%)	19 (49%)	33 (63%)
Remittive	30 (60%)	20 (62%)	34 (74%)
Palindromic	2 (50%)	1 (33%)	2 (50%)
Single flare	8 (38%)	9 (69%)	7 (47%)
TOTAL	75 (59%)	49 (56%)	78 (65%)

* not statistically significant

TABLE 6.8 Clinical characteristics and indices according to gender

	Females (n=90)		Males (n=38)		p value	
Age at onset	51.0	(13.7)	53.2	(12.5)	0.39	
Nodules	27	(30%)	16	(42%)	0.26	
N° tender joints	3.1	(3.6)	3.3	(3.8)	0.78	
Tenderness index	3.7	(4.2)	3.6	(4.1)	0.96	
N° swollen joints	4.8	(6.1)	3.5	(4.2)	0.24	
Articular index	7.0	(10.2)	4.4	(5.8)	0.14	
N° limited joints	5.2	(6.0)	5.3	(5.1)	0.92	
ROM index	6.2	(7.6)	6.5	(6.9)	0.86	
Pain scale (VAS)	30.8	(25.2)	26.2	(16.9)	0.33	
Morning stiffness	43.8	(66.2)	32.1	(50.1)	0.33	
Hand deformities	28	(31%)	7	(18%)	0.21	
X-ray score	5.8	(6.9)	7.5	(10.6)	0.29	
MHAQ-ADL	0.49	(0.47)	0.50	(0.46)	0.85	
ESR	26.2	(15.8)	19.6	(12.8)	0.04	*
Hemoglobin	13.0	(1.4)	14.7	(1.5)	0.001	*
Positive ANA(n=119)	56	(67%)	22	(63%)	0.85	

Continuous variables shown as mean (SD)
* statistically significant

TABLE 6.9 Clinical characteristics and joint counts according to type of onset

	TYPE OF ONSET			
	Gradual (n=94)	**Acute** (n=20)	**Palindromic** (n=14)	**p value**
Age at onset	52.1 (12.8)	53.7 (15.9)	45.6 (12.7)	0.18
Nº females (%)	70 (29%)	2 (10%)	6 (43%)	0.09
Nº tender joint	3.6 (4.0)	2.1 (2.3)	2.0 (1.5)	0.13
Tenderness index	4.2 (4.6)	2.5 (2.6)	2.0 (1.5)	0.08
Nº swollen joints	4.7 (8.9)	4.3 (5.2)	2.4 (3.3)	0.37
Articular index	6.7 (9.8)	6.2 (8.3)	2.9 (3.7)	0.34
Nº limited joints	5.6 (5.9)	4.4 (4.8)	3.9 (5.4)	0.48
ROM index	6.9 (7.7)	4.6 (4.9)	4.9 (7.6)	0.34
Nodules	28 (30%)	7 (35%)	8 (57%)	0.13
Hand deformities	27 (29%)	2 (10%)	6 (43%)	0.09

Continuous variables shown as mean (SD)

TABLE 6.10 Other outcome measures, ANA, RF, and HLA DR4 according to type of onset

	TYPE OF ONSET			
	Gradual (n=94)	**Acute** (n=20)	**Palindromic** (n=14)	**p value**
Pain scale (VAS)	31.6 (23.5)	23.6 (23.8)	23.9 (17.9)	0.26
Morning stiffness	41.5 (56.7)	43.5 (83.8)	28.2 (63.4)	0.74
Radiological score	6.6 (7.6)	5.3 (4.2)	6.0 (14.5)	0.80
MHAQ-ADL	0.52 (0.49)	0.42 (0.45)	0.39 (0.32)	0.50
Positive RF (n=127)	55 (59%)	13 (65%)	7 (50%)	0.68
Positive ANA (n=119)	56 (64%)	14 (74%)	8 (62%)	0.70
HLA DR4 (n=87)	39 (58%)	7 (50%)	3 (50%)	0.81
Hemoglobin	13.3 (1.6)	13.6 (1.9)	14.3 (1.5)	0.14
ESR	25.5 (15.1)	25.0 (17.2)	16.2 (11.2)	0.14

Continuous variables shown as mean (SD)

TABLE 6.11 Clinical characteristics and indices according to RF status (127 patients)

	Neg RF (n=52)		**Pos RF** (n=75)		**p value**	
Age at onset	53.3	(13.9)	50.2	(12.8)	0.20	
N° females (%)	39	(75%)	51	(68%)	0.51	
Nodules	10	(19%)	33	(44%)	0.007	*
N° tender joints	2.8	(3.7)	3.5	(3.7)	0.33	
Tenderness index	3.1	(3.9)	4.1	(4.3)	0.21	
N° swollen joints	2.4	(3.1)	5.8	(6.5)	0.001	*
Articular index	3.1	(4.6)	8.5	(10.8)	0.001	*
N° limited joints	4.8	(5.4)	5.5	(6.0)	0.53	
ROM index	5.7	(6.8)	6.7	(7.7)	0.44	
Pain	27.99	(24.2)	30.7	(22.7)	0.53	
Morning Stiffness	37.0	(59.7)	43.1	(63.9)	0.59	
Hand deformities	13	(25%)	22	(29%)	0.74	
Xray score	5.4	(9.4)	7.0	(7.3)	0.30	
MHAQ-ADL	0.50	(0.48)	0.49	(0.46)	0.94	
ESR	20.6	(13.1)	27.1	(16.2)	0.03	*
Hemoglobin	13.7	(1.4)	13.4	(1.8)	0.30	
Positive ANA	24	(50%)	54	(76%)	0.006	*

* statistically significant
Continuous variables shown as mean (SD)

TABLE 6.12 Clinical characteristics and indices according to HLA DR4 status (87 patients)

	Neg DR4 (n=38)		**Pos DR4** (n=49)		p value
Age at onset	49.4	(14.2)	51.6	(12.7)	0.46
N° females	23	(60%)	36	(73%)	0.29
Nodules	15	(39%)	16	(32%)	0.67
Positive RF	19	(50%)	28	(57%)	0.66
RF titres	90.5	(149.6)	142.0	(289.1)	0.29
N° tender joints	4.1	(4.3)	3.1	(3.9)	0.32
Tenderness index	4.7	(4.7)	3.5	(4.3)	0.22
N° swollen joints	6.1	(6.5)	3.8	(5.3)	0.07
Articular index	9.2	(12.0)	5.1	(7.7)	0.06
N °limited joints	5.9	(5.1)	5.2	(5.8)	0.54
ROM index	6.8	(6.2)	6.6	(8.2)	0.87
Pain scale (VAS)	28.7	(20.8)	29.7	(23.5)	0.83
Morning stiffness	57.5	(81.6)	41.9	(62.2)	0.31
Hand deformities	10	(26%)	15	(31%)	0.84
Xray score	6.2	(6.0)	6.4	(9.9)	0.93
MHAQ-ADL	0.52	(0.47)	0.50	(0.47)	0.87
ESR	25.0	(18.6)	22.6	(13.8)	0.52
Hemoglobin	13.5	(1.6)	13.7	(1.7)	0.55
Positive ANA	22	(58%)	37	(75%)	0.13

Continuous variables shown as mean (SD)

TABLE 6.13 Clinical characteristics and indices according to the presence of rheumatoid nodules

	No nodules (n=85)		**Nodules** (n=43)		**p value**	
Age at onset	53.8	(12.9)	47.4	(13.4)	0.009	*
N° females	63	(74%)	27	(63%)	0.26	
N° tender joints	2.9	(3.5)	3.7	(4.0)	0.30	
Tenderness index	3.5	(4.1)	4.0	(4.4)	0.67	
N° swollen joints	3.0	(3.7)	7.2	(7.4)	0.001	*
Articular index	4.0	(5.8)	10.6	(12.5)	0.001	*
N° limited joints	4.4	(5.5)	6.8	(5.9)	0.03	*
ROM index	5.1	(6.4)	8.7	(8.5)	0.009	*
Pain	30.1	(24.2)	28.2	(21.1)	0.68	
Morning Stiffness	41.8	(59.8)	37.6	(66.5)	0.72	
Hand deformities	16	(19%)	19	(44%)	0.005	*
Xray score	4.8	(6.1)	9.3	(10.5)	0.002	*
MHAQ-ADL	0.50	(0.47)	0.47	(0.47)	0.69	
ESR	23.9	(15.6)	25.5	(14.9)	0.60	
Hemoglobin	13.3	(1.7)	13.8	(1.6)	0.17	
Positive ANA (n=119)	49	(65%)	29	(71%)	0.51	

* statistically significant
Continuous variables shown as mean (SD)

TABLE 6.14 Clinical characteristics and indices according to education and economic status

	Education (n=126)		Income (n=121)	
Age at onset	-0.44 (p<0.001)	*	-0.45 (p<0.001)	*
Sex	-0.10 (p=0.26)		-0.04 (p=0.69)	
RF titres	0.10 (p=0.29)		0.07 (p=0.47)	
N° tender joints	-0.17 (p=0.06)		-0.19 (p=0.03)	*
Tenderness index	-0.18 (p=0.05)	*	-0.21 (p=0.02)	*
N° swollen joints	-0.06 (p=0.53)		-0.02 (p=0.84)	
Articular index	-0.07 (p=0.43)		-0.01 (p=0.96)	
N° limited joints	-0.17 (p=0.06)		-0.15 (p=0.10)	
ROM index	-0.11 (p=0.21)		-0.10 (p=0.29)	
Pain	-0.17 (p=0.07)		-0.18 (p=0.06)	
Morning stiffness	-0.00 (p=1.00)		0.07 (p=0.47)	
Hand deformities	-0.13 (0=0.16)		-0.08 (p=0.36)	
Xray score	-0.06 (p=0.50)		-0.11 (p=0.21)	
MHAQ-ADL	-0.25 (p=0.004)	*	-0.36 (p<0.001)	*
ESR	-0.16 (p=0.09)		-0.14 (p=0.14)	
Hemoglobin	0.02 (p=0.81)		-0.05 (p=0.59)	

Results reported as two-tailed correlations
*statistically significant

TABLE 6.15 Demographic and clinical characteristics according to marital status

	Married (n=88)		**Single *** (n=40)		**p value**
Age at onset	50.7	(12.6)	53.7	(14.9)	0.24
N° females (%)	56	(64%)	34	(85%)	0.24
Nodules	29	(33%)	14	(35%)	0.99
RF	56	(64%)	19	(48%)	0.11
RF titre	118	(254)	149	(270)	0.53
DR4	30	(52%)	19	(66%)	0.32
N° tender joints	3.0	(3.3)	3.5	(4.3)	0.54
Tenderness index	3.4	(3.6)	4.2	(5.2)	0.33
N° swollen joints	4.1	(4.9)	5.1	(6.8)	0.37
Articular index	5.7	(8.0)	7.3	(11.2)	0.37
N° limited joints	4.8	(5.6)	6.1	(5.9)	0.27
ROM index	5.9	(7.2)	7.2	(7.6)	0.34
Hand deformities	24	(27%)	11	(27%)	1.00
Xray score	6.2	(7.2)	6.6	(10.0)	0.76
MHAQ-ADL	0.46	(0.45)	0.57	(0.49)	0.22
ESR	23.1	(13.1)	27.1	(18.7)	0.18
Hemoglobin	13.6	(1.7)	13.2	(1.5)	0.17
Education	11.4	(2.8)	10.9	(3.1)	0.38
Income **	4.9	(2.0)	2.6	(1.1)	0.001
ANA	52	(65%)	26	(67%)	1.00

Continuous variables shown as mean (SD)
* single includes never married, separated, divorced and widowed
** statistically significant

TABLE 6.16. Correlation matrix for outcome measures

	TDJ	**SWJ**	**ROMJ**	**ESR**	**XRAY**	**MHAQ**
TDJ	1.00					
SWJ	0.55 p<0.001*	1.00				
ROMJ	0.31 p<0.001*	0.53 p<0.001*	1.00			
ESR	0.27 p=0.004*	0.38 p<0.001*	0.39 p<0.001*	1.00		
XRAY	0.14 p=0.113	0.36 p<0.001*	0.53 p<0.001*	0.09 p=0.33	1.00	
MHAQ	0.54 p<0.001*	0.32 p<0.001*	0.38 p<0.001*	0.28 p=0.003*	0.15 p=0.093	1.00

TDJ: number of tender joints - SWJ: number of swollen joints
ROMJ: number of limited join areas - XRAY: Xray score
* statistically significant

CHAPTER 7

RESULTS 3

THERAPY

1. CURRENT USE OF SECOND-LINE DRUGS

For this analysis, the following drugs were considered second-line: antimalarials, auranofin, parenteral gold compounds, methotrexate, D-penicillamine, azathioprine, sulfasalazine and cyclophosphamide. Although there are some other experimental drugs and therapies, none of the patients in the cohort had received any treatment that could be included as such. All patients on parenteral gold compounds therapy were receiving sodium aurothiomalate (GSTM).

At the time of the study, 78 patients (61%) were receiving second-line drugs. Seventy patients (90% of those receiving remittive therapy) were receiving a single drug , 8 were receiving 2 drugs and 1 patient a combination of 3. Overall, 78 patients were receiving 88 drug therapies (8 different drugs).

Frequency of current use for the different second-line drugs is shown in Table 7.1. GSTM was the most commonly administered drug, followed by methotrexate and antimalarials. Overall, gold compounds (GSTM and auranofin) were being administered to one third of the patients in the cohort, accounting for 44% of all drugs.

2. CHARACTERISTICS OF THE USE OF SECOND-LINE DRUGS DURING THE COURSE OF THE DISEASE

2.1 SECOND-LINE DRUGS PRESCRIBED

One hundred and nine patients (85.2%) had received at least one second-line drug at any time during the average 6.5 years of disease.

Overall, the different second-line drugs had been used by the following numbers of patients:

1. GSTM:	70 patients	(54.7%)
2. Auranofin:	37 patients	(28.9%)
3. Sulfasalazine:	33 patients	(25.8%)
4. Antimalarials:	32 patients	(25.0%)
5. Methotrexate:	27 patients	(21.1%)
6. D-penicillamine:	25 patients	(19.5%)
7. Azathioprine:	6 patients	(4.7%)
8. Cyclophosphamide:	3 patients	(2.3%)

At the time of the study, 46% of the patients had received at least 2 second-line drugs. Total numbers of second-line drugs received were as follows:

None	19 patients	(14.8%)
1 drug	50 patients	(39.1%)
2 drugs	26 patients	(20.3%)
3 drugs	17 patients	(13.3%)
4 drugs	8 patients	(6.3%)
5 or more	8 patients	(6.3%)

Overall, a total of 233 second-line drug therapies were reported in 109 patients.

2.2 COMBINATION THERAPY

Table 7.2 shows how often the second-line drugs were used alone and how often in combination. Cyclophosphamide and azathioprine were almost invariably used in combination with other second-line drugs. Sulfasalazine and antimalarials had been given in combination almost 40% of the times. Gold compounds, D-penicillamine and methotrexate were prescribed as single drugs in the majority of patients. Altogether, 76% of all second-line drugs prescribed had been given as sole remittive agent.

Twenty-four patients (18%) received a total of 29 combined therapies (26 2-drug combinations and 3 3-drug combinations). The following 2-drug combinations were used:

- sulfasalazine-D-penicillamine (6 patients)
- antimalarials-GSTM (5 patients)
- sulfasalazine-GSTM (3 patients)
- antimalarials-methotrexate (3 patients)
- sulfasalazine-auranofin (2 patients)
- sulfasalazine-methotrexate (1 patient)
- sulfasalazine-antimalarials (1 patient)
- GSTM-methotrexate (1 patient)
- D-penicillamine-methotrexate (1 patient)
- sulfasalazine-azathioprine (1 patient)
- antimalarials-azathioprine (1 patient)
- methotrexate-azathioprine (1 patient).

Only 1 3-drug combination was used:

- cyclophosphamide-azathioprine-antimalarials (3 patients)

2.3 SELECTION OF FIRST SECOND-LINE DRUG

Of the 109 patients that received second-line therapy during the course of the disease, 6 received GSTM and 7 methotrexate as their first remittive agent, as part of a controlled double-blind trial of 6 months duration. For the following tabulation, these patients were excluded since the purpose of the analysis was to determine which drugs were most often selected by rheumatologists as the first remittive therapy. The 96 other patients that had been treated received the following drugs as first second-line therapy:

- GSTM:	38 patients	(40%)
- Auranofin:	24 patients	(25%)
- Antimalarials:	18 patients	(19%)
- Sulfasalazine:	14 patients	(15%)
- Penicillamine:	2 patients	(2%)

Gold compounds were the first drug of choice for 65% of these patients. Cytotoxic drugs and methotrexate were never chosen as first remittive therapy (as mentioned before, methotrexate had been given as first drug to 7 patients in a clinical trial).

Figure 7.1 shows the year of start of the first second-line drug. Over 50% of the patients started second-line therapy within the first 2 years of RA (1985-86).

2.4 CHOICE OF SECOND-LINE DRUGS DURING THE COURSE OF THE DISEASE

Table 7.3 summarizes the order in which the different second-line drugs were chosen for therapy. Since the purpose of this tabulation was to define the overall preferences of physicians regarding therapy, the 13 patients participating in the gold-methotrexate study were excluded from this particular analysis. Significant differences were observed among the different drugs (p=0.001). Gold compounds (both auranofin and GSTM) were chosen as 1st or 2nd drugs most of the times they were prescribed: 93% of the prescriptions for GSTM were as 1st or 2nd choice. Antimalarials and sulfasalazine were also prescribed as 1st or 2nd choice approximately two thirds of the times they were used. Methotrexate and penicillamine were administered most often as 2nd or 3rd choice. Cyclophosphamide and azathioprine were only given after a minimum of 3 other drugs had been tried.

2.5 PHYSICIANS' VARIATIONS IN USE OF SECOND-LINE DRUGS

For this analysis, only rheumatologists practicing in Edmonton in 1986 were included. The reason for this selection was based on the impression that rheumatologists who started their practices after 1986 would treat patients at a later point in time and the results would not reflect their usual practice, since newly diagnosed patients from the 1985 cohort would not have had the opportunity to consult them during the first years of disease. Again, the 13 patients participating in the trial were excluded.

Six rheumatologists were included in the analysis. They had prescribed 210 of the total 233 drugs (90%). Table 7.4 shows the frequencies with which the second-line drugs were prescribed by the various rheumatologists. Significant differences were observed in the patterns of prescription. All the rheumatologists prescribed most often either antimalarials or gold compounds. Those prescribing gold compounds generally chose GSTM. Only one rheumatologist administered oral gold more often than the parenteral compounds. Statistically significant differences were observed among rheumatologists in the use of chloroquine, auranofin and sulfasalazine.

A similar analysis was conducted for the first second-line drug prescribed (Table 7.5). All rheumatologists had chosen either gold or antimalarials as first second-line drug in most patients. Four physicians chose one of the 2 gold compounds in the majority of cases (50 to 80%). Two of these chose GSTM more often, 1 auranofin and the other chose the 2 drugs with equal frequency. Another physician chose gold and antimalarials with similar frequency. The remaining rheumatologist prescribed antimalarials as the first remittive drug in 60% of the patients. One physician prescribed sulfasalazine as first second-line drug in one third of the patients.

Second-line therapy was occasionally initiated by non-rheumatologist physicians. Seven of the total 233 drug treatments were initiated by general or family practitioners, or internists. These physicians prescribed a variety of drugs: antimalarials (2), auranofin (1), GSTM (1), methotrexate (1), d-penicillamine (1) and sulfasalazine (1).

2.6 DURATION OF THERAPY

Since the second-line drugs were given at different points in time, duration of therapy was estimated not only as mean duration in months, but also as number of person-years (PY). Results were as follows [mean in months, (SD), PY]:

GSTM	25.9	(26.4)	151 PY
Auranofin	19.5	(17.2)	60 PY
Antimalarials	24.9	(21.5)	66 PY

Sulfasalazine	14.9 (16.9)	41 PY
D-penicillamine	18.0 (15.9)	37 PY
Methotrexate	28.1 (25.19)	63 PY
Azathioprine	9.2 (14.3)	5 PY
Cyclophosphamide	2.3 (2.3)	0.6 PY

2.7 DISCONTINUATION OF SECOND-LINE THERAPIES

Table 7.6 shows the causes for discontinuation of the different drugs. Overall, 144 of the 233 drugs prescribed (62%) had been discontinued. The most frequent cause for discontinuation was inefficacy (42% of withdrawals, 26% of all treatments), followed by toxicity (35% of withdrawals, 22% of all treatments). In 7% of the cases the drug had been discontinued by the patient (12% of all discontinuations). A statistically significant difference was observed among the different drugs. Toxicity was the main reason for discontinuing GSTM (52% of withdrawals). For auranofin, antimalarials, sulfasalazine and methotrexate the basis for termination was inefficacy. The lowest rate of discontinuations due to toxicity was observed for methotrexate (10% of terminations, $p=0.006$).

Survival time analysis was conducted following the Kaplan-Meier product limit method to calculate the proportion of patients still receiving the various drugs at different points in time. Table 7.7 shows the percentages of patients still on each drug at 6, 12, 18 and 24 months. In general, discontinuations for methotrexate were less common than for other drugs, and achieved statistical significance at 12 months when compared with GSTM and sulfasalazine, and at 24 months when compared with sulfasalazine. Sulfasalazine had the lowest proportion of patients continuing therapy at all cut points; the differences, however, were significant only when compared to methotrexate. Table 7.8 shows the percentages of patients continuing on the same drug at 30, 36, 42 and 48 months. Again, methotrexate rates were higher than for other drugs and achieved statistical significance when compared to sulfasalazine (30-48 months), penicillamine (36-48 months) and auranofin (30 months)

Frequency of side effects is shown on Table 7.9. Rates were calculated using person-years in the denominator to control for differences in duration of disease.

2.8 EFFICACY OF SECOND-LINE DRUGS

The evaluation of efficacy in an observational study may be subject to the confounding effects of the severity of the disease prior to therapy. For that reason, the association of outcome measures to therapy was evaluated in 2 ways: by analyzing all patients in the cohort, and by analyzing only those patients who had received second-line drugs ('intent to treat').

Patients who had not received remittive therapy scored significantly better than treated patients for number of tender joints, number of swollen joints, restricted joint areas and MHAQ. Radiological scores, however, were similar for both groups (6.1 in the non-treated and 6.4 in the treated). The duration of second-line therapy (including all drugs and all patients) was not correlated with most variables. A positive correlation was observed only for the number of restricted joint areas.

In the second step, data were analyzed according to 'intent to treat', including only those patients who had received second-line therapy. The outcome measures were examined in treated patients, in relation to the duration of therapy with the different drugs. Correlations are shown in Table 7.10. Statistically significant negative correlations were observed for almost every outcome measure and duration of therapy with GSTM.

Treated patients were categorized in 2 groups: those having received remittive therapy (any drug) for a total duration of 1 year or less, and those treated for more than 1 year. No significant differences were observed for any of the outcome measures. The same analysis was performed for GSTM. Results are shown in Table 7.11. Significant differences were observed for the number of swollen joints, swollen joint index, ESR, hemoglobin and radiological score, with patients having received the drug for over a year scoring better on these measures.

None of the other drugs were examined, since the numbers of treated patients were substantially smaller than for GSTM, and there was no evidence of a potential association from the bivariate correlations (Table 7.10)

3. USE OF CORTICOSTEROIDS

Eleven patients were receiving prednisone at the time of the assessment; however, in 2, the reason for corticosteroid therapy was not RA (cataract surgery and Graves disease respectively). Overall, 9 out of 128 patients (7.0%) were on corticosteroid therapy for their arthritis, receiving a mean dose of 6.7mg/day (range 3-15mg).

Twenty-five patients (19.5%) had received oral corticosteroids at some point in time during the course of the disease. Only 20 (15.6%) had received the steroids as treatment of RA (2 received prednisone for concomitant diseases and 3 for treatment of side effects from RA-related therapies).

Ninety-four patients (73%) stated that they had received intraarticular or soft-tissue corticosteroid injections.

4. UTILIZATION OF SOME HEALTH SERVICES

4.1 CONSULTS TO RHEUMATOLOGISTS

Patients had seen a rheumatologist for the first time as follows:

- 1985	62 patients	(48.4%)
- 1986	35 patients	(27.3%)
- 1987	16 patients	(12.5%)
- 1988	6 patients	(4.7%)
- 1989	5 patients	(3.9%)
- 1990	3 patients	(2.3%)
- 1991	1 patient	(0.8%)

Eighty-four patients (65%) had seen a single rheumatologist during the course of the disease, 38 (30%) had seen 2, 4 (3%) had seen 3, and the rest (2%) had seen 4 or more.

Average number of consults to a rheumatologist varied considerably among patients. To compute the mean number of visits, a maximum of 12 visits per year was allowed. This adjustment was made because some of the patients would go for parenteral gold or methotrexate injections to their rheumatologists. Since the consults would vary according to schedule, holidays etc., patients on regular therapy were equally assessed, and assigned a maximum of a visit per month. The average number of visits to a rheumatologist, during the course of the disease, from 1985 to 1991 was

14.7 (±15.7). In general, the number of visits was stable over the 7 years, averaging slightly over 2 visits per year (each year calculated separately).

4.2 OTHER

Only 7 patients (5%) did not have insurance covering the cost of drugs. The rest had coverage ranging from 70 to 100% of the total cost of drugs.

Twenty-five patients (20%) had been admitted to hospital at least once because of their RA. Approximately one-quarter of those admitted (6 patients) had 2 or more RA-related admissions.

Forty-eight patients (37%) had attended one of the available patient education programs offered by the different hospitals in the city. Approximately half of these had attended the program during the first 2-3 years of disease (1987 or earlier).

Ninety patients (70%) had utilized physical therapy services at least once during the course of the disease.

Twenty-nine patients (23%) followed a therapeutic exercise routine regularly, at least 3 times per week. Twenty-four patients (19%) did the exercise routine less than 3 times per week. The rest (58%) never exercised. Forty-five percent of the patients however, stated that they engaged in a recreational exercise activity such as walking, running or sports at least once a week.

5. SURGERY

Twenty-five patients (20%) had one or more joint or joint-related surgery procedures. Surgical procedures were as follows:

Carpal tunnel release	8 patients	(6%)
Knee joint replacement	6 patients	(5%)
Synovectomy	3 patients	(2%)
Fracture-related surgeries	3 patients	(2%)
Hip joint replacement (not fracture-related)	2 patients	(2%)
Tenotomy	2 patients	(2%)

- Hallux valgus corrections, extensor tendon rupture repair and arthrodesis were performed in 1 patient each.

Two of the knee arthroplasties were thought to be primarily done for osteoarthritis of the knee, preceding RA. Two of the 3 fractures requiring surgery were fractures of the hip.

Two patients underwent radiochemical synovectomies of the knees.

6. ALTERNATIVE MEDICINE

Twenty-eight patients (22%) described use of homeopathic remedies. Among these, several different kinds had been used. Often, patients did not remember the exact name of the different substances tried and referred to them as 'herbs' or 'teas'. For this reason, it was difficult to establish frequency of use of the specific alternative remedies.

Among others, patients described use of alfalfa, aloe vera, devil's claw and a variety of plant-extracted oils.

Fourteen patients (11%) had received acupuncture as therapy for RA.

No significant differences were observed in the joint indices, radiological and functional scores between patients who had used alternative remedies and patients who did not.

Patients reporting the use of homeopathic medicine were younger (age at onset 44 years vs. 54 years, p=0.001), had a higher education level (12.4 vs. 10.9, p=0.015) and higher total household income (5.0 vs 3.9, p=0.013). Marital status and gender were similar for both groups. No differences were observed for these factors between patients reporting acupuncture therapy and those not reporting this therapy.

TABLE 7.1 Current use of second-line drugs

DRUGS	N° PTS	% ALL PTS[*]	% ALL DRUGS[**]
GSTM	26	20.3%	29.9%
Methotrexate	17	13.3%	19.5%
Antimalarials	14	10.9%	16.1%
Auranofin	12	9.4%	13.8%
Sulfasalazine	8	6.2%	9.2%
D-penicillamine	7	5.5%	8.0%
Azathioprine	2	1.6%	2.3%
Cyclophosphamide	1	0.8%	1.1%

* percentage calculated over total number of patients (128)
** percentage calculated over total number of therapies (87)

TABLE 7.2. Use of second-line drugs during the course of RA

DRUG	TOTAL	ALWAYS AS SOLE DRUG	SOMETIMES COMBINED	ALWAYS COMBINED
GSTM	70	62 (89%)	6 (8%)	2 (3%)
Auranofin	37	35 (94%)	1 (3%)	1 (3%)
Sulfasalazine	33	20 (61%)	6 (18%)	7 (21%)
Antimalarials	32	20 (62%)	7 (22%)	5 (16%)
Methotrexate	27	21 (78%)	6 (22%)	-
D-penicillamine	25	18 (72%)	4 (16%)	3 (12%)
Azathioprine	6	-	1 (17%)	5 (83%0)
Cyclophosphamide	3	-	-	3 (100%)
Total	233*	176 (76%)	31 (13%)	26 (11%)

Chi-square=83.3, $p<0.0001$
* total number of drug therapies, in the 128 patients

TABLE 7.3 Choice of different second-line drugs during the course of RA

DRUG (n)	1st	2nd	3rd	4th	≥5th
GSTM (64)	38 (59%)	21 (33%)	4 (6%)	1 (1%)	-
Auranofin (37)	24 (65%)	7 (19%)	4 (11%)	-	2 (5%)
Sulfasalazine (33)	14 (42%)	7 (21%)	9 (39%)	3 (9%)	-
Antimalarials (32)	18 (56%)	4 (13%)	3 (9%)	6 (19%)	1 (3%)
Methotrexate (20)	-	7 (35%)	6 (22%)	4 (15%)	3 (11%)
Penicillamine (25)	2 (2%)	13 (22%)	8 (32%)	1 (4%)	1 (4%)
Azathioprine (6)	-	-	-	3 (50%)	3 (50%)
Cyclophosphamide (3)	-	-	-	-	3(100%)
TOTAL	96	59	34	18	13

13 patients participating in a gold-methotrexate study were excluded from the analysis
Percentages calculated over row totals

TABLE 7.4 Prescription of second-line drugs by different rheumatologists

RHEUMATOLOGIST	**1**	**2**	**3**	**4**	**5**	**6**
GSTM	4 (17%)	18 (31%)	4 (40%)	8 (27%)	7 (30%)	22 (33%)
Auranofin *	1 (4%)	-	2 (20%)	12 (40%)	3 (13%)	18 (27%)
Sulfasalazine **	2 (9%)	16 (28%)	-	1 (3%)	1 (4%)	11 (17%)
Antimalarials ***	9 (39%)	4 (7%)	4 (40%)	4 (13%)	4 (17%)	3 (4%)
Penicillamine	3 (13%)	9 (15%)	-	2 (7%)	3 (13%)	7 (11%)
Methotrexate	3 (13%)	5 (9%)	-	2 (7%)	5 (22%)	4 (6%)
Azathioprine	1 (4%)	3 (5%)	-	1 (3%)	-	1 (1%)
Cyclophosphamide	-	3 (15%)	-	-	-	-
TOTAL	23	58	10	30	23	66

* p=0.02 - ** p=0.01 - *** p<0.0001 (compared to all other drugs combined)
Percentages calculated over column totals (total number of drugs prescribed by each physician)

TABLE 7.5 Prescription of first second-line drugs by different rheumatologists

RHEUMATOLOGIST	**1**	**2**	**3**	**4**	**5**	**6**
GSTM	3 (30%)	12 (54%)	2 (25%)	4 (33%)	5 (50%)	12 (40%)
Auranofin	-	-	2 (25%)	7 (58%)	3 (30%)	12 (40%)
Sulfasalazine	1 (10%)	8 (36%)	-	-	-	4 (13%)
Antimalarials *	6 (60%)	1 (5%)	4 (50%)	1 (8%)	2 (20%)	1 (3%)
Penicillamine	-	1 (5%)	-		-	1 (3%)
TOTAL	10	22	8	12	10	30

* $p < 0.0001$, when compared to all other drugs combined
Percentages calculated over column totals (total number of drugs prescribed by each physician)

TABLE 7.6 Discontinuation of second-line drugs

			REASON FOR DISCONTINUATION **					
DRUGS	N	TOTAL* N° DC	SIDE *** EFFECTS	INEFFICACY	NO LONGER NEEDED	DC BY PATIENT	CONCOMITANT DISEASE	UNKNOWN
GSTM	70	44 (63%)	23 (52%)	16 (36%)	1	4	-	-
Auranofin	37	25 (68%)	5 (20%)	12 (48%)	3	4	-	1
Sulfasalazine	33	24 (73%)	6 (25%)	11 (46%)	1	4	-	2
Antimalarials	32	17 (53%)	4 (24%)	6 (35%)	3	3	1	-
Methotrexate	27	10 (37%)	1 (10%)	5 (50%)	1	-	2	1
Penicillamine	25	18 (72%)	8 (44%)	9 (50%)	-	1	-	-
Azathioprine	6	4 (67%)	2 (50%)	1 (25%)	-	1	-	-
Cyclophosphamide	3	2 (67%)	2(100%)	-	-	-	-	-
TOTAL	233	144 (62%)	51 (35%)	60 (42%)	9 (6%)	17 (12%)	3 (2%)	4 (3%)

DC discontinuation - * percentage calculated over n, differences not significant
** percentage calculated over total # discontinuations
*** $p=0.006$

TABLE 7.7 Survival time analysis for various second-line drugs (6 to 24 months)

	SURVIVAL 6M	SURVIVAL 12M	SURVIVAL 18M	SURVIVAL 24M
GSTM	67% [55.5-77.8]	53% [40.8-64.7]	50% [37.6-61.6]	42% [30.4-54.7]
Auranofin	75% [61.1-89.3]	64% [47.6-79.4]	51% [34.1-67.8]	37% [20.5-54.2]
Sulfasalazine	59% [41.4-76.0]	46% [28.1-63.2]	36% [18.6-52.6]	24% [8.0-39.5]
Antimalarials	81% [66.9-94.6]	71% [54.5-86.8]	63% [45.2-80.5]	58% [40.3-76.9]
Methotrexate	81% [66.3-96.1]	81% [66.3-96.1]	70% [50.6-89.3]	64% [42.3-84.8]
D-penicillamine	72% [53.7-89.4]	57% [36.9-77.6]	48% [26.9-68.5]	38% [17.7-58.6]

Results shown as percentage of patients still on drug [95% CI]

TABLE 7.8 Survival time analysis for various second-line drugs (30 to 48 months)

	SURVIVAL 30M		**SURVIVAL 36M**		**SURVIVAL 42M**		**SURVIVAL 48M**	
GSTM	41%	[28.6-52.9]	41%	[28.6-52.9]	39%	[26.7-50.9]	37%	[24.8-49.0]
Auranofin	25%	[8.8-41.0]	21%	[5.4-36.1]	21%	[5.4-36.1]	21%	[5.4-36.1]
Sulfasalazine	20%	[4.8-34.7]	13%	[* - 27.7]	13%	[* - 27.7]	13%	[* - 27.7]
Antimalarials	53%	[33.9-72.7]	43%	[22.3-63.0]	43%	[22.3-63.0]	36%	[14.3-56.7]
Methotrexate	64%	[42.3-84.8]	56%	[33.6-79.4]	56%	[33.6-79.4]	56%	[33.6-79.4]
D-penicillamine	33%	[12.6-52.8]	16%	[* -32.9]	16%	[* -32.9]	16%	[* -32.9]

Results shown as percentage of patients still on drug [95% CI]
* negative lower bound

TABLE 7.9 Frequency of side effects for the different drugs

DRUG	N	(PY)	N° PTS WITH SE	SE PER 100 PY *
GSTM	70	(151)	31 (44%)	20.5
Auranofin	37	(60)	13 (35%)	21.7
Sulfasalazine	33	(41)	8 (24%)	19.5
Antimalarials	32	(66)	6 (23%)	9.0
Methotrexate	27	(63)	7 (26%)	11.1
Penicillamine	25	(37)	11 (44%)	29.3
Azathioprine	6	(5)	3 (50%)	65.2

N: N° patients - PY: person-years - SE: side effects
* p=0.03

TABLE 7.10 Correlations between duration of therapy with the different drugs and outcome measures

	Nº Tender joints	Nº Swollen joints	Nº Restricted joints	X-ray score	MHAQ
GSTM (70)	0.06 p=0.50	-0.38 p=0.001*	-0.28 p=0.02*	-0.26 p=0.03*	-0.08 p=0.52
Auranofin (37)	-0.08 p=0.50	-0.10 p=0.55	0.14 p=0.40	-0.06 p=0.72	-0.32 p=0.05*
Sulfasalazine (33)	0.03 p=0.75	-0.07 p=0.70	-0.06 p=0.76	0.28 p=0.12	0.05 p=0.77
Antimalarials (32)	-0.10 p=0.24	-0.29 p=0.11	-0.29 p=0.11	-0.03 p=0.88	-0.40 p=0.02*
Methotrexate (27)	0.11 p=0.23	-0.20 p=0.33	-0.25 p=0.21	-0.15 p=0.44	-0.24 p=0.24
Penicillamine (25)	0.20 p=0.02	0.04 p=0.84	0.00 p=1.00	0.04 p=0.84	0.06 p=0.78
All 2nd line (108) combined	-0.01 p=0.90	-0.05 p=0.60	0.07 p=0.56	0.09 p=0.37	-0.11 p=0.25

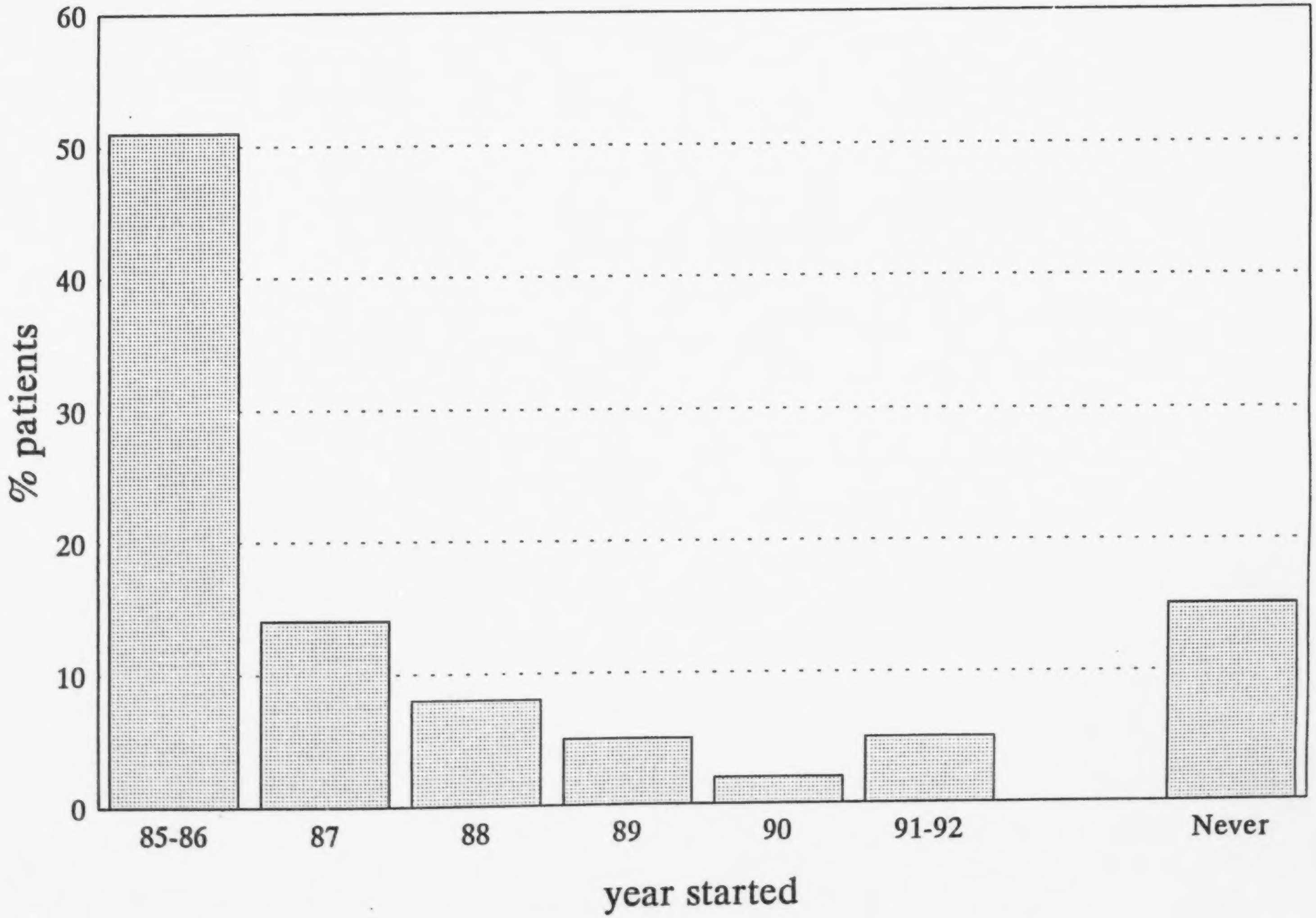
* statistically significant

TABLE 7.11 Duration of therapy with GSTM and outcome measures in 70 patients treated with GSTM

OUTCOME MEASURES	DT ≤ 1yr (n=35)		DT > 1yr (n=35)		p value	
N° tender joints	4.4	(3.9)	3.3	(4.3)	0.26	
Tenderness index	5.0	(4.4)	3.5	(4.6)	0.18	
N° swollen joints	8.0	(7.4)	2.9	(4.3)	0.001	*
Swollen joints index	11.4	(12.3)	3.7	(5.8)	0.002	*
N° restricted joints	8.8	(6.9)	5.2	(5.0)	0.02	*
ROM index	10.2	(8.4)	6.1	(6.4)	0.02	*
ESR	32.3	(14.2)	20.1	(12.1)	0.001	*
Hemoglobin	12.7	(1.6)	13.9	(1.3)	0.001	*
Radiological score	9.5	(11.8)	4.5	(4.1)	0.02	*
MHAQ-ADL	0.62	(0.43)	0.56	(0.52)	0.63	

* statistically significant

Figure 7.1 Year of initiation of second-line therapy



CHAPTER 8

RESULTS 4

MULTIVARIATE ANALYSIS

MULTIPLE LINEAR REGRESSION

Linear multiple regression methods were used as a first step to examine the associations of different variables with the current clinical status and outcome of RA while controlling for potential confounders.

The initial assumptions and theoretical framework postulated that the various types of outcome measures represented different dimensions of the overall prognosis. Following this hypothesis, different models were examined for each of the outcome dimensions.

1. DISEASE ACTIVITY

A variety of indices have been proposed to measure disease activity in patients with RA (Chapter 2). For the multivariate analyses the number of swollen joints was used as the dependent variable to assess disease activity.

The following independent variables were included in the regression models:

- Gender - gender was included as a dichotomous variable with the values:
  0 = female
  1 = male

- Age at onset, in years - given the nature of the population study, this was equivalent to age (r=0.99).

- Duration of disease - the possible values for this variable were limited to 6 or 7 years, so it was interpreted as a dichotomous variable with no attempt to extrapolate results as in the case of a continuous variable.

- RF - patients were considered seropositive if a titre $\geq$1/40 had been recorded at any point in time during the course of the disease or/and at the time of ascertainment. This variable was dichotomous with the values:

  0 = negative

  1 = positive

- Rheumatoid nodules - this variable was dichotomous with the values:

  0 = no history of rheumatoid nodules

  1 = present or past history of rheumatoid nodules

- Education level - Education level was measured on an ordinal scale with possible values ranging from 0 to 18 (Appendix 7). For this analysis, it was considered as a continuous variable.

- Total household income for 1990 - Total household income was measured on an ordinal scale with possible values ranging from 1 to 8 (Appendix 7). For this analysis, it was considered as a continuous variable.

- Current marital status - Marital status was entered in the models as a dichotomous variable with the values:

  0 = married

  1 = single, widowed or divorced

- Year of initial consult with a rheumatologist - this variable was entered as continuous and recoded as follows:

  1 = 1985 or 1986

  2 = 1987

  3 = 1988

  4 = 1989

5 = 1990

6 = 1991 or 1992

- Year of initiation of second-line therapy - this variable was entered as continuous and recoded as follows:

1 = 1985 or 1986

2 = 1987

3 = 1988

4 = 1989

5 = 1990

6 = 1991 or 1992

7 = never initiated second-line therapy

Initially all the variables listed above were included in the model. Stepwise regression was used to select only those variables with statistically significant coefficients. Model 1 in Table 8.1 shows the obtained results. The presence of nodules and seropositivity for RF were the only variables significantly associated with the number of swollen joints. This model was based on 121 patients since 7 of them had missing values for the variable 'reported income'. Table 8.2 shows a different model, obtained by entering RF, nodules, gender, age at onset and disease duration as independent variables. This model was based on the 128 patients in the cohort and showed an independent effect of gender, with females scoring higher in number of swollen joints.

The interaction term between nodules and RF was not statistically significant.

2. ARTICULAR DAMAGE

For this analysis, radiological scores were included as a measure of radiological damage. Since the theoretical framework for the study was based on the hypothesis that articular damage was influenced by the degree of disease activity, the number of swollen joints was entered as an independent variable in these models. In addition, all the independent variables described above also were included. Table 8.3 shows the initial model obtained by stepwise regression. The number of swollen joints showed the strongest association with radiological damage. Duration of disease also showed a significant association, with patients with 7 years of disease presenting a higher score of radiological damage.

In subsequent models, the number of swollen joints and the presence of nodules were removed one at a time and then together to analyze the effect of seropositivity. No significant associations were observed for RF as a dichotomous variable. In some models, however, a significant association was noted when RF titres were included as a continuous variable. This association became insignificant when the presence of nodules or the number of swollen joints were added to the model.

3. FUNCTIONAL STATUS

Functional status was measured with the MHAQ-ADL score. In the models evaluating function as an outcome, all the independent variables described above were included. The radiological score and the various joint indices (number of swollen joints, number of tender joints and number of limited joints) also were added to the models. This was based on the hypothesis that function was dependent on articular damage and disease activity. Table 8.4 shows the stepwise regression model.

Significant associations were observed for the number of tender joints, the number of limited joints and total household income. When some of the other joint indices were removed, a significant association with the number of swollen joints was observed. The interaction between education and income was significant when added to the model (p=0.0017) suggesting a multiplicative effect of education and income combined, with patients in the lower brackets for both variables being at higher risk than if the effects were simply added. Interactions between income and number of tender joints and income and number of limited joints were not statistically significant.

4. OTHER MODELS

Various other models also were tested including RF titres instead of RF as a dichotomous variable. The only differences observed were for radiological scores as the dependent variable, where, as noted above, RF was only significantly associated when included as titres.

Models also were tested on the subgroup of patients having either a chronic or a remittive course. Results were generally similar to the ones already described.

Table 8.1 Linear multiple regression model (stepwise method) with the number of swollen joints as dependent variable (MODEL 1)

	B	SE	ß	p value		R²
Constant	1.88	(0.76)		0.014	*	
Nodules	3.53	(1.03)	0.30	0.0009	*	0.12
RF	2.43	(0.98)	0.22	0.015	*	0.17
Variables not in equation						
Age at onset			0.02	0.84		
Gender			-0.17	0.07		
Education			-0.07	0.43		
Income			-0.11	0.23		
Marital status			0.11	0.20		
Disease duration			0.10	0.26		
Yr seen by rheumatologist			0.04	0.66		
Yr started 2nd-line drugs			-0.02	0.82		

* statistically significant
B: partial regression coefficient; SE: standard error of B;
ß: standardized regression coefficients (for variables not in the equation, resulting if variable were entered next);
R^2: coefficient of determination as variables are entered

TABLE 8.2 Linear multiple regression model with the number of swollen joints as dependent variable (MODEL 2)

	B	SE	ß	p value	
Constant	-6.62	(6.43)		0.31	
Nodules	3.7	(1.02)	0.32	0.0004	*
RF	2.78	(0.96)	0.25	0.004	*
Gender (males)	-2.07	(1.01)	-0.17	0.04	*
Age at onset	0.03	(0.04)	0.06	0.48	
Disease duration	1.14	(0.92)	0.10	0.21	

* statistically significant
B: partial regression coefficient; SE: standard error of B;
ß: standardized regression coefficients

TABLE 8.3 Linear multiple regression model (stepwise method) with the radiological score as dependent variable

	B	**SE**	**ß**	**p value**		**R^2**
Constant	-20.71	(9.52)		0.03	*	
Nº swollen jts	0.42	(0.13)	0.29	0.002	*	0.13
Disease duration	2.87	(1.39)	0.17	0.04	*	0.15
Nodules	3.27	(1.60)	0.19	0.04	*	0.18
Age at onset	0.10	(0.05)	0.18	0.05	*	0.20
Variables not in equation						
RF			-0.03	0.75		
Gender			0.08	0.37		
Education			0.03	0.76		
Income			-0.04	0.69		
Marital status			-0.02	0.81		
Yr seen by rheumatologist			0.02	0.82		
Yr started 2nd-line drugs			0.06	0.45		

* statistically significant

B: partial regression coefficient; SE: standard error of B;

ß: standardized regression coefficients (for variables not in the equation, resulting if variable were entered next);

R^2: coefficient of determination as variables are entered

Table 8.4 Linear multiple regression model (stepwise method) with the MHAQ-ADL score as dependent variable

	B	SE	ß	p value		R^2
Constant	0.44	(0.09)		<0.0001	*	
N° tender jts	0.06	(0.01)	0.47	<0.0001	*	0.33
Income	-0.05	(0.02)	-0.23	0.002	*	0.39
N° limited joints	0.02	(0.006)	0.20	0.009	*	0.43
Variables not in equation						
Age at onset			0.12	0.15		
Gender			0.05	0.48		
RF			-0.006	0.94		
Nodules			-0.07	0.36		
Education			-0.08	0.29		
Marital status			-0.09	0.29		
N° swollen jts			-0.04	0.68		
Radiological score			-0.07	0.43		
Disease duration			0.05	0.47		
Yr seen by rheumatologist			0.02	0.82		
Yr started 2nd-line drugs			0.06	0.45		

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* statistically significant
B: partial regression coefficient; SE: standard error of B;
ß: standardized regression coefficients (for variables not in the equation, resulting if variable were entered next);
R^2: coefficient of determination as variables are entered

CHAPTER 9

RESULTS 5

MULTIVARIATE ANALYSIS

LOGISTIC REGRESSION

The distribution of some of the variables used in the multiple regression models was not normal, showing marked skewness to the right (chapter 6). Since this can result in a violation of the assumptions related to multiple linear regression methods, the models were analyzed using logistic regression procedures with categorized data. Again, the 3 outcome dimensions examined were: a) disease activity, b) articular damage and c) functional status.

1. DISEASE ACTIVITY

The number of swollen joints was used as a measure of disease activity. Patients were categorized according to the median cut-off point, as follows:

0 - low: 0 to 2 swollen joints (normal or mild disease activity) - 64 patients

1 - high: 3 to highest number of swollen joints (moderate to severe disease activity) - 64 patients

The following independent variables were categorized as dichotomous, as follows:

a) gender

0 - male

1 - female

b) age at onset

0 - $\leq$ 52 years of age at onset

1 - $>$ 52 years of age at onset

c) duration of disease

0 - 6 years

1 - 7 years

d) total household income for 1990

0 - low, < 35,000 /year

1 - high, ≥ 35,000/year

e) education level at interview

0 - low, grade 11 or less

1 - high, grade 12 or more

f) current marital status

0 - married

1 - single, widowed or divorced

g) rheumatoid factor

0 - negative

1 - positive (at any time during the course of RA)

h) rheumatoid nodules

0 - absent

1 - positive (at any time during the course of RA)

Table 9.1 shows the categorization of the independent variables according to the number of swollen joints treated as a dichotomous variable. The OR's and probability values were calculated listwise for all 128 patients for most variables, and pairwise for variables with missing values. Significant unadjusted ORs were observed for a positive history of nodules (3.0) and seropositivity for RF (2.1).

Table 9.2 shows the multiple logistic regression results when all of the independent variables were forced into the model (121 cases). Gender and a history of rheumatoid nodules were the 2 variables that reached statistical significance. Male gender had a protective effect with an OR of 0.39. A history of nodules gave an OR of approximately 3.

For subsequent models, variables were removed one at a time, according to the probability value of the coefficients (backwards elimination procedure). The final model had gender and a history of rheumatoid nodules as independent associations. Odds ratios were as follows (OR [95% confidence bounds, p value]):

Male gender	0.40	[0.19 - 0.85, p=0.02]
Nodules	3.01	[1.45 - 6.27, p=0.003]

Because of the known association of RF with nodules in RA, additional models were examined, removing the presence of nodules. The final model after the removal of nodules as an independent variable included gender and rheumatoid factor. Odds ratios were as follows (OR [95% confidence intervals, p value]):

Male gender	0.45	[0.21 - 0.98, p=0.04]
Positive RF	1.84	[1.08 - 3.14, p=0.025]

The presence of nodules was the strongest factor associated with number of swollen joints, with an OR of 3. Models incorporating RF without including rheumatoid nodules as a variable, resulted in an increased risk of 1.8 for seropositivity. This risk, however, was not independent of the risk associated with the presence of nodules and the effect became insignificant when this last variable was reentered. Males had a better outcome than females in relation to the number of swollen joints, with a protective OR of approximately 0.4.

2. ARTICULAR DAMAGE

To study outcome in relation to articular damage, the radiological score was used as a dependent variable. Once again, the outcome variable was dichotomized according to the value of the distribution closest to the median as follows:

- 0 - low: 0 to 4 (normal or mild damage) - 71 patients
- 1 - high: 5 to highest score (moderate to severe damage) - 55 patients

Variables included in these models were the same as above with the addition of the number of swollen joints as a dichotomous variable. The purpose of this addition was to test the hypothesis that disease activity as measured by the number of swollen joints was associated with radiological damage.

Table 9.3 shows the distribution of patients and unadjusted OR's for the different predictors according to radiological score status (low and high). Statistically significant OR's were observed for disease duration, RF, history of nodules and number of swollen joints. Table 9.4 shows the logistic regression model resulting from forcing all of the independent variables into the equation. Significant coefficients were observed for age at onset, income and the number of swollen joints. Although the coefficient for income showed borderline significance, the direction of the association was not consistent with the expected effect, since patients with higher incomes had an increased risk for radiological damage. Income lost its statistical significance and was removed from the model when backward elimination procedures were used.

Table 9.5 shows various logistic regression models according to the different predictors entered. Model 1 shows the final model for all variables entered in the first step (Table 9.4), after using backward elimination procedures. Disease duration showed a significant association with radiological damage, with an OR for a high radiological score of 2.8 for 7 years compared to 6 years. Since the models including the number of swollen joints as a dependent variable had shown an association with nodules and RF, a new model was run, excluding this variable (Model 2). The duration of disease remained a significant association. The presence of nodules was also significantly associated with higher radiological scores. Rheumatoid factors were not significantly associated when nodules were included in the model. When nodules were excluded, a statistically significant OR for RF (2.6) was obtained (Model 3).

3. FUNCTIONAL STATUS

Functional status as measured by the MHAQ-ADL index was dichotomized according to the value closest to the median as follows:

0 - Low score: 0 to 0.375 (normal function or mild disability) - 65 patients

1 - High score: 0.376 to highest (moderate to severe disability) - 62 patients

Table 9.6 shows the categorization of patients and unadjusted ORs for the different independent variables according to functional status. Significant differences were observed for age at onset, number of swollen joints, number of tender joints, number of limited joints, income and education. Table 9.7 shows the logistic regression model obtained by forcing all variables into the model. Significant results were observed for income (OR: 0.23), number of tender joints (OR: 10.1) and number of limited joints (OR: 5.4). Table 9.8 (Model 1) shows the final results using a backwards elimination procedure. The three significant variables included by this method were as before: income (OR: 0.24), number of tender joints (OR: 8.5) and number of limited joints (OR: 3.1). In Model 2, income was substituted by education: although the OR showed a protective effect (0.55), it did not achieve statistical significance. Model 3 was similar to Model 1, but controlled for age at onset. Since the unadjusted OR for age had been significant, the effect of controlling for age was thought to be important, since the relationship between age and function was considered reasonable on theoretical grounds. No significant changes were observed in relation to Model 1.

TABLE 9.1 Categorization of patients according to the number of swollen joints (low, high) and predictor variables

	Nº SWOLLEN JOINTS			
	LOW (n=64)	**HIGH (n=64)**	**OR**	**p value**
1. Gender				
female	41	49		
male	23	15	0.55	0.18
2. Age at onset				
≤ 52	33	32		
> 52	31	32	1.1	1.00
3. Disease duration				
6 yrs	32	32		
7 yrs	32	34	1.1	0.86
4. Income(n=121)				
low	37	38		
high	22	24	1.0	1.00
5. Education (n=126)				
low	27	30		
high	35	34	0.87	0.84
6. Marital status				
married	44	44		
single/widowed/divorced	20	20	1.0	1.00
7. RF(n=127)				
negative	32	20		
positive	31	44	2.1	0.04 *
8. Nodules				
absent	50	35		
positive	14	29	3.0	0.009 *

OR: odds ratio
* statistically significant

TABLE 9.2 Logistic regression model using the number of swollen joints (low vs high) as outcome variable

	B	SE	OR	95%CI	p value	
Constant	-0.29	(0.64)			0.65	
Gender	-0.94	(0.47)	0.39	[0.15 - 0.99]	0.05	*
Age at onset	0.10	(0.48)	1.1	[0.43 - 2.8]	0.83	
Disease duration	0.30	(0.40)	1.3	[0.62 - 2.9]	0.45	
Income	-0.22	(0.57)	0.80	[0.26 - 2.5]	0.70	
Education	-0.26	(0.44)	0.77	[0.33 - 1.8]	0.55	
Marital status	-0.26	(0.51)	0.77	[0.29 - 2.1]	0.61	
Rheumatoid factor	0.64	(0.42)	1.9	[0.84 - 4.3]	0.12	
Nodules	1.09	(0.45)	3.0	[1.2 - 7.2]	0.02	*

B: coefficient; SE: standard error of coefficient
OR: odds ratio; CI: confidence bounds for OR;
* statistically significant

TABLE 9.3 Categorization of patients according to the radiological score (low, high) and predictor variables

	RADIOLOGICAL SCORE			
	LOW (n=68)	HIGH (n=51)	OR	p value
1. Gender				
female	50	39		
male	21	16	0.98	1.00
2. Age at onset				
≤ 52	41	24		
> 52	30	31	1.8	0.16
3. Disease duration				
6 yrs	41	20		
7 yrs	30	35	2.4	0.03 *
4. Income (n=120)				
low	43	31		
high	25	21	1.2	0.83
5. Education (n=125)				
low	27	29		
high	43	26	0.56	0.16
6. Marital status				
married	49	37		
single/widowed/divorced	22	18	1.1	0.98
7. RF				
negative	35	16		
positive	36	38	2.0	0.04 *
8. Nodules				
absent	54	29		
positive	17	26	2.8	0.01 *
9. N° swollen joints				
low	51	12		
high	20	43	9.1	<0.0001 *

OR: odds ratio
* statistically significant

TABLE 9.4 Logistic regression model using the radiological score (low vs high) as outcome variable

	B	SE	OR	95%CI	p value	
Constant	-3.57	(0.91)			<0.001	*
Gender	-0.15	(0.58)	0.86	[0.28 - 2.7]	0.80	
Age at onset	1.30	(0.60)	3.7	[1.1 - 11.9]	0.03	*
Disease duration	0.89	(0.48)	2.4	[0.95 - 6.2]	0.06	
Income	1.37	(0.71)	3.9	[0.97 -16.0]	0.05	*
Education	-0.67	(0.53)	0.51	[0.18 - 1.4]	0.20	
Marital status	0.89	(0.63)	2.4	[0.71 - 8.3]	0.16	
Rheumatoid factor	0.46	(0.51)	1.5	[0.58 - 4.3]	0.37	
Nodules	0.54	(0.53)	1.7	[0.61 - 4.8]	0.31	
N° swollen joints	2.32	(0.51)	10.1	[3.7 - 27.4]	<0.001	*

B: coefficient; SE: standard error of coefficient;
OR: odds ratio; CI: confidence bounds for OR
* statistically significant

TABLE 9.5 Selected logistic regression models using the radiological score (low vs high) as outcome variable

	B	SE	OR	95%CI	p value
MODEL 1					
Constant	-2.04	(0.43)			<0.001 *
Disease duration	1.04	(0.43)	2.8	[1.2 - 6.6]	0.017 *
Nº swollen joints	2.30	(0.44)	9.9	[4.2 - 23.4]	<0.001 *
MODEL 2					
Constant	-1.52	(0.41)			<0.001 *
Disease duration	0.91	(0.39)	2.5	[1.2 - 5.3]	0.021 *
Nodules	0.89	(0.41)	2.4	[1.09 - 5.5]	0.030 *
RF	0.74	(0.41)	2.1	[0.94 - 4.7]	0.072
MODEL 3					
Constant	-1.34	(0.40)			<0.001 *
Disease duration	0.94	(0.38)	2.6	[1.2 - 5.4]	0.014 *
RF	0.94	(0.40)	2.6	[1.2 - 5.6]	0.017 *

B: coefficient; SE: standard error of coefficient;
OR: odds ratio ; CI: confidence bounds for OR
* statistically significant

TABLE 9.6 Categorization of patients according to the MHAQ-ADL score (low, high) and predictor variables

	MHAQ-ADL SCORE			
	LOW (n=65)	HIGH (n=62)	OR	p value
1. Gender				
female	46	44		
male	19	18	1.3	1.00
2. Age at onset				
≤ 52	41	24		
> 52	24	38	2.7	0.01 *
3. Disease duration				
6 yrs	35	27		
7 yrs	24	35	1.5	0.33
4. Income (n=121)				
low	28	47		
high	31	15	0.29	0.002 *
5. Education(n=126)				
low	23	26		
high	41	28	0.41	0.05 *
6. Marital status				
married	48	39		
single/widowed/divorced	17	23	1.7	0.26
7. RF (n=126)				
negative	25	26		
positive	39	36	0.89	0.88
8. Nodules				
absent	42	42		
positive	23	20	0.87	0.85
9. N° swollen joints				
low	39	24		
high	26	38	2.4	0.03 *
10. N° tender joints				
low	51	17		
high	14	45	9.6	0.0001 *
11. N° limited joints				
low	45	18		
high	20	44	5.5	0.0001 *

OR: odds ratio
* statistically significant

TABLE 9.7 Logistic regression model using the MHAQ-ADL score (low vs high) as outcome variable

	B	SE	OR	95%CI	p value	
Constant	-0.65	(0.83)			0.43	
Gender	-0.27	(0.60)	0.77	[0.23 - 2.5]	0.66	
Age at onset	-0.32	(0.63)	0.72	[0.21 - 2.5]	0.61	
Disease duration	0.63	(0.48)	1.9	[0.73 - 4.9]	0.19	
Income	-1.46	(0.73)	0.23	[0.06 - 1.0]	0.05	*
Education	-0.35	(0.54)	0.70	[0.25 - 2.0]	0.51	
Marital status	-0.13	(0.68)	0.88	[0.23 - 3.3]	0.84	
Rheumatoid factor	-0.17	(0.53)	0.84	[0.30 - 2.4]	0.74	
Nodules	-0.29	(0.57)	0.75	[0.25 - 2.3]	0.61	
N° swollen joints	-0.52	(0.62)	0.60	[0.18 - 2.0]	0.40	
N° tender joints	2.31	(0.55)	10.1	[3.4 - 29.5]	<0.001	*
N° limited joints	1.68	(0.58)	5.4	[1.7 - 16.6]	0.004	*

B: coefficient; SE: standard error of coefficient;
OR: odds ratio; CI: confidence bounds for OR
* statistically significant

TABLE 9.8 Logistic regression models using the MHAQ-ADL score (low vs high) as outcome variable.

	B	SE	OR	95%CI	p value
MODEL 1					
Constant	-0.96	(0.38)			0.013 *
Income	-1.43	(0.49)	0.24	[0.09 - 0.62]	0.003 *
Nº tender joints	2.14	(0.48)	8.5	[3.3 - 21.8]	<0.001 *
Nº limited joints	1.13	(0.46)	3.1	[1.3 - 7.6]	0.014 *
MODEL 2					
Constant	-1.19	(0.42)			0.005 *
Education	-0.60	(0.43)	0.55	[0.23-1.3]	0.17
Nº tender joints	1.91	(0.44)	6.8	[2.9-15.9]	<0.001 *
Nº limited joints	1.17	(0.44)	3.2	[1.4-7.6]	0.007 *
MODEL 3					
Constant	-0.96	(0.49)			0.05 *
Income	-1.44	(0.55)	0.24	[0.08-0.70]	0.009 *
Nº tender joints	2.14	(0.48)	8.5	[3.3-22.0]	<0.001 *
Nº limited joints	1.13	(0.47)	3.1	[1.2-7.8]	0.015 *
Age at onset	-0.009	(0.52)	0.99	[0.35-2.8]	0.99

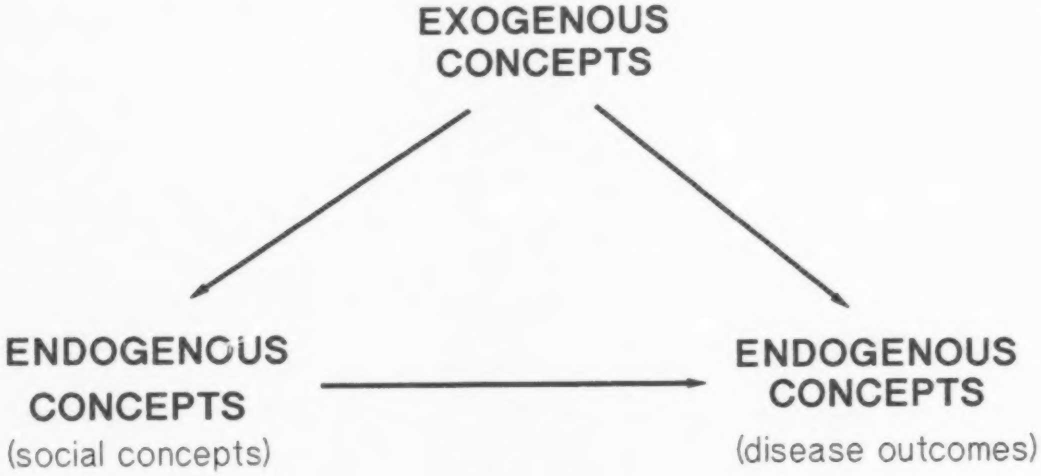
B: coefficient; SE: standard error of coefficient;
OR: odds ratio; CI: confidence bounds for OR
* statistically significant

CHAPTER 10

RESULTS 6

LISREL MODELS

The last step in the multivariate analysis was based on the use of structural equation modeling to combine some of the previous findings. The LISREL program was used to analyze the data. In general, all models tested were based on the following diagram:


EXOGENOUS CONCEPTS
ENDOGENOUS CONCEPTS
(social concepts)
ENDOGENOUS CONCEPTS
(disease outcomes)

Several models were tested to investigate the potentially causal associations between various factors and the clinical status and outcome measures. The following variables were used for these models:

- age
- gender
- marital status
- total household income
- education level
- RF
- number of swollen joints
- radiological score

- MHAQ-ADL

The selection of variables was based on: 1) the theoretical framework for the study of the causal links, 2) the observed results from the previous analyses with the data, 3) the reliability and validity of variables as known from the available published evidence.

1. MODEL 1

Figure 10.1 depicts the first model tested.

The model was based on 8 concepts, 4 exogenous and 4 endogenous. Each concept had a single indicator based on the measured variables. The variances of the errors in the measured variables were fixed, based on the reliability of the different measures.

The following exogenous concepts (*ksis*) were included:

CONCEPT	**INDICATOR**	**ERROR σ^2**
1. Age	Reported age in years	0%
2. Sex	Reported sex 0 - female 1 - male	0%
3. Marital status	Reported marital status 0 - married	0%

	1 - single, widowed, divorced, separated	0%
4. RF	Seropositivity for RF 0 - negative 1 - positive	10%

The following endogenous concepts (*etas*) were included:

CONCEPTS	**INDICATORS**	**ERROR σ^2**
1. Education	Reported education level scored from 1 to 18	10%
2. Income	Reported total household income scored from 1 to 8	10%
3. Disease activity	Number of swollen joints measured in physical examination	10%
4. Functional status (disability)	Reported MHAQ-ADL scores	10%

The hypothetical causal mechanisms underlying the proposed model are as follows: 1) age and sex have an effect on income and education, 2) the level of education is related to the income, 3) RF and sex have an effect on disease activity, and 4) education, income, age and disease activity relate to the functional status of patients. Sex, RF and marital status have only an indirect effect on physical disability through their links with other variables.

Results obtained for this LISREL model are shown in Appendix 8. The resulting measures of goodness of fit were as follows:

- Chi-square with 10 degrees of freedom: 9.81
- Probability level for chi-square: 0.46
- Goodness of fit index: 0.981
- Adjusted goodness of fit index: 0.974
- Root mean square residual: 0.297

Structural coefficients ß (effect of endogenous concepts on other endogenous concepts) and Γ (effects of exogenous concepts on endogenous concepts), having adjusted for reliability of the indicators are shown in Figure 10.2. Most coefficients were statistically significant. The presence of RF, which can be considered a marker for the biological component of the disease, was significantly associated with disease activity, with patients with positive RF having an increased disease activity. Overall, functional status had significant independent links with disease activity and income. Disease activity had a significant effect on functional status, with higher levels of disease activity related to disability. The effect of RF on functional status was indirect through its increase in disease activity. Income was associated with physical disability, with lower total household incomes related to poor functional outcome (high MHAQ-ADL score). Marital status was significantly associated with income, with single individuals having less income, and indirectly having a decreased functional status. Age, which was significantly associated with income and education had indirect links to disability through these variables. The direct effect of age on function, although insignificant, was kept in the model because its importance has been described by others (chapter 2). Other insignificant effects also were kept in the model for controlling purposes. This was based on evidence from previous studies: the effect of sex and age on education and income is well recognized. The effect of sex on disease activity also has been described by others, with females showing a worse prognosis; since this was consistent with the present model and borderline in significance for a one-tailed t-test, the coefficient was retained. The effect of education on function also was included. This effect was small and insignificant, and the link to function was mostly indirect through income. Lower education was related to lower income and thus linked to disability. The insignificant direct effect was, however, kept in the model for controlling other coefficients because other investigators have suggested an association (chapter 2).

The squared multiple correlations for the dependent variables in the different structural equations were as follows:

- education: 0.22
- income: 0.56
- disease activity: 0.13
- functional status: 0.28

The best explained endogenous concept was income, followed by functional status. Yet, since some insignificant effects were included in the model, the overall squared correlations and coefficient of determination should probably be smaller.

Overall the model showed a general pattern of biological effects (sex and RF) directly affecting disease activity and disease activity determining factional status in conjunction with various social factors.

2. MODEL 2

The latent concept of articular damage had not been included in the previous model. In this model, a new endogenous latent concept was introduced replacing disease activity. This new concept that was named 'disease severity' had two indicators (Figure 10.2):

- the number of swollen joints as measured by physical examination

- the radiological scores, as measured according to the methods previously outlined.

In this model, the concept 'severity' was measured in the units of the number of swollen joints in order to facilitate comparisons with the previous one. The error variance in the indicator 'number of swollen joints' was again fixed at 10%, and the error variance in the radiological score was left free to be estimated by LISREL. The remaining concepts and indicators, and parameters to be estimated were kept similar to the previous model. In general, all structural coefficients were similar in size and statistical significance to the ones in the previous model. The chi-square with 17 degrees of freedom was 15.98 ($p=0.52$). The LISREL estimation of the measurement error proportion in the variance of the indicator 'radiological score' was 88%. Since this was extremely high in comparison to the known validity and reliability of the radiological changes in RA, the model was not considered acceptable.

3. MODEL 3

In this model, radiological damage was entered as a new endogenous latent concept with the indicator 'radiological score'. This model had the same four exogenous concepts with their single indicators, as in the previous models. These included: age, sex, marital status and RF. Again, the indicators of the first three concepts were given 0% of error variance, and the indicator of RF, 10%. Five endogenous concepts were included, with single indicators for each as follows:

CONCEPT	**INDICATOR**	**ERROR σ^2**
Education	as before	10%
Income	as before	10%
Disease activity	number of swollen joints	10%
Radiological damage	radiological score	10%
Functional status	MHAQ-ADL score	10%

Figure 10.4 depicts this model with the resulting structural coefficients. Results are included in Appendix 9. In this model again, RF was significantly associated with disease activity. An increase in disease activity was related to an increase in both radiological damage and disability. The effects of RF on function and radiological damage were indirect through its effect on disease activity. Although these data did not support a direct effect, the coefficient between RF and radiological damage was kept in the model because of the association described in the literature (chapter 2). Most of these publications, however, were based on bivariate analyses and did not seek an indirect effect through disease activity as observed in this model. These data suggest that the effect is only indirect. The direct and indirect effects of the demographic and social concepts on functional status were generally similar to the observed in Model 1. A different model was fit including an effect on function from radiological damage. The coefficient was insignificant and small; therefore, it was decided to exclude it.

The measures of goodness of fit for this model were as follows:

- Chi-square with 15 degrees of freedom: 13.39
- Probability level for chi-square: 0.57

- Goodness of fit index: 97.7
- Adjusted goodness of fit index 0.97
- Root mean square residual: 0.34

The squared multiple correlations for the dependent variables in the different structural equations were as follows:

- education: 0.22
- income: 0.56
- disease activity: 0.12
- radiological damage: 0.18
- functional status: 0.28

The analysis of the LISREL results (modification indices and partial derivatives) showed that if other ß and Γ coefficients were added to the model, they would not attain statistical significance.

In relation to Model 2, when radiological damage was included as a new concept, the magnitude of the gain in explanatory power was somewhat small. Eighty-two percent of the variance was unexplained in this model. When the radiological score had been included as a second indicator of severity (Model 2), the error variance estimated by LISREL was 88%.

In terms of the fit, this model could be considered slightly better than Model 1, since it had more degrees of freedom, increasing the parsimony of the model, with equivalent probability and goodness of fit.

Different error variances for various indicators were examined in this last model, one at a time. The proportion of the variance attributed to error was fixed first at 5% and then at 20% for all those variables in which some error in the measurement had been adjusted for (RF, education level, reported income, number of swollen joints, radiological score and MHAQ-ADL score). No major changes were observed, either in the magnitude or significance of the coefficients.

In summary, this model suggests that two distinct outcome dimensions occur in RA, one related to function and the other to joint damage, as evidenced by the radiological changes. The activity of the disease, which appears to be basically biological in origin, has an effect on both of these outcome concepts. Social variables, on the other hand, have significant direct and indirect associations with physical disability.

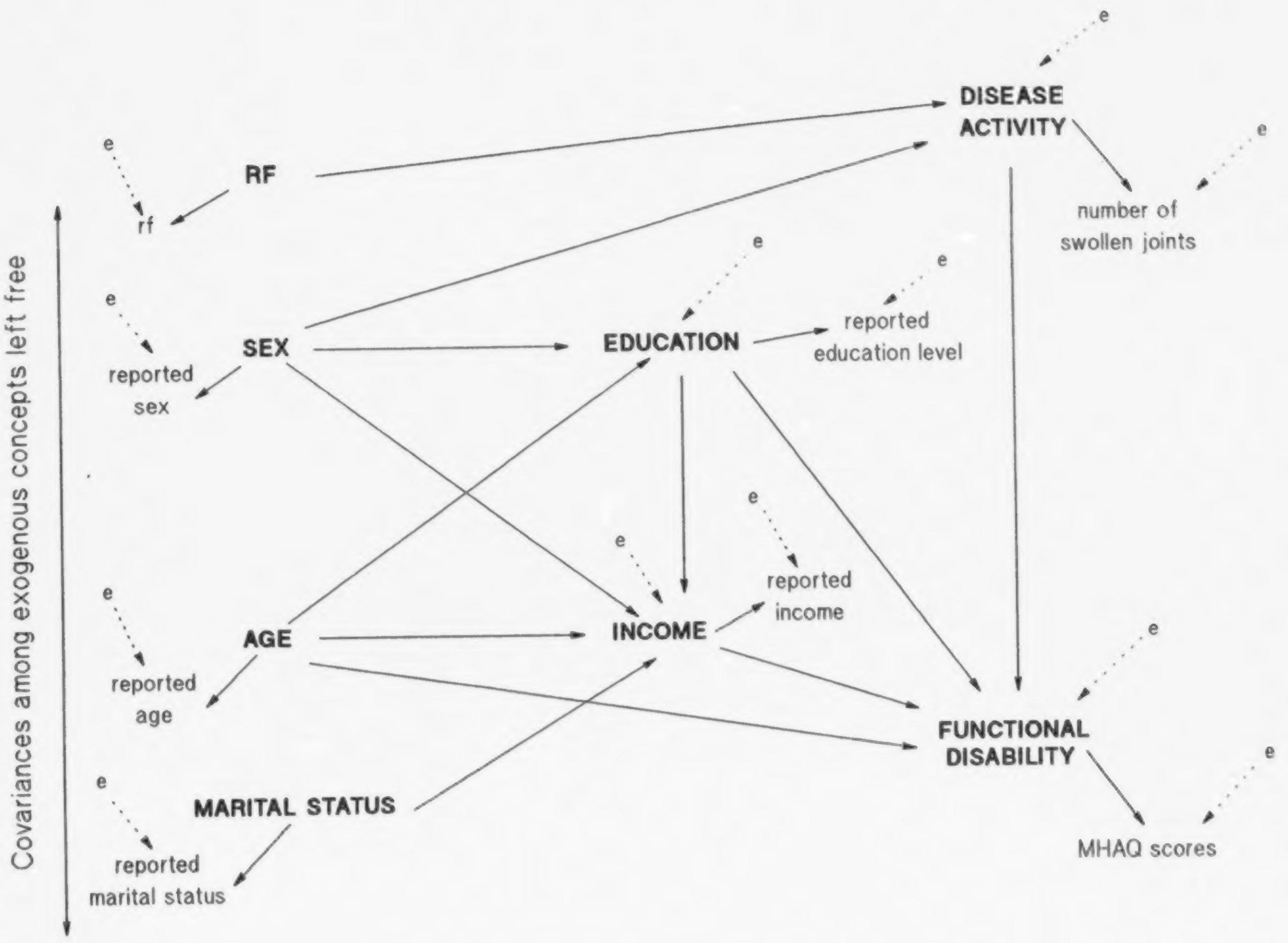

DISEASE ACTIVITY
number of swollen joints
RF
rf
SEX
reported sex
EDUCATION
reported education level
INCOME
reported income
AGE
reported age
MARITAL STATUS
reported marital status
FUNCTIONAL DISABILITY
MHAQ scores
e
Covariances among exogenous concepts left free

Figure 10.1. LISREL model 1

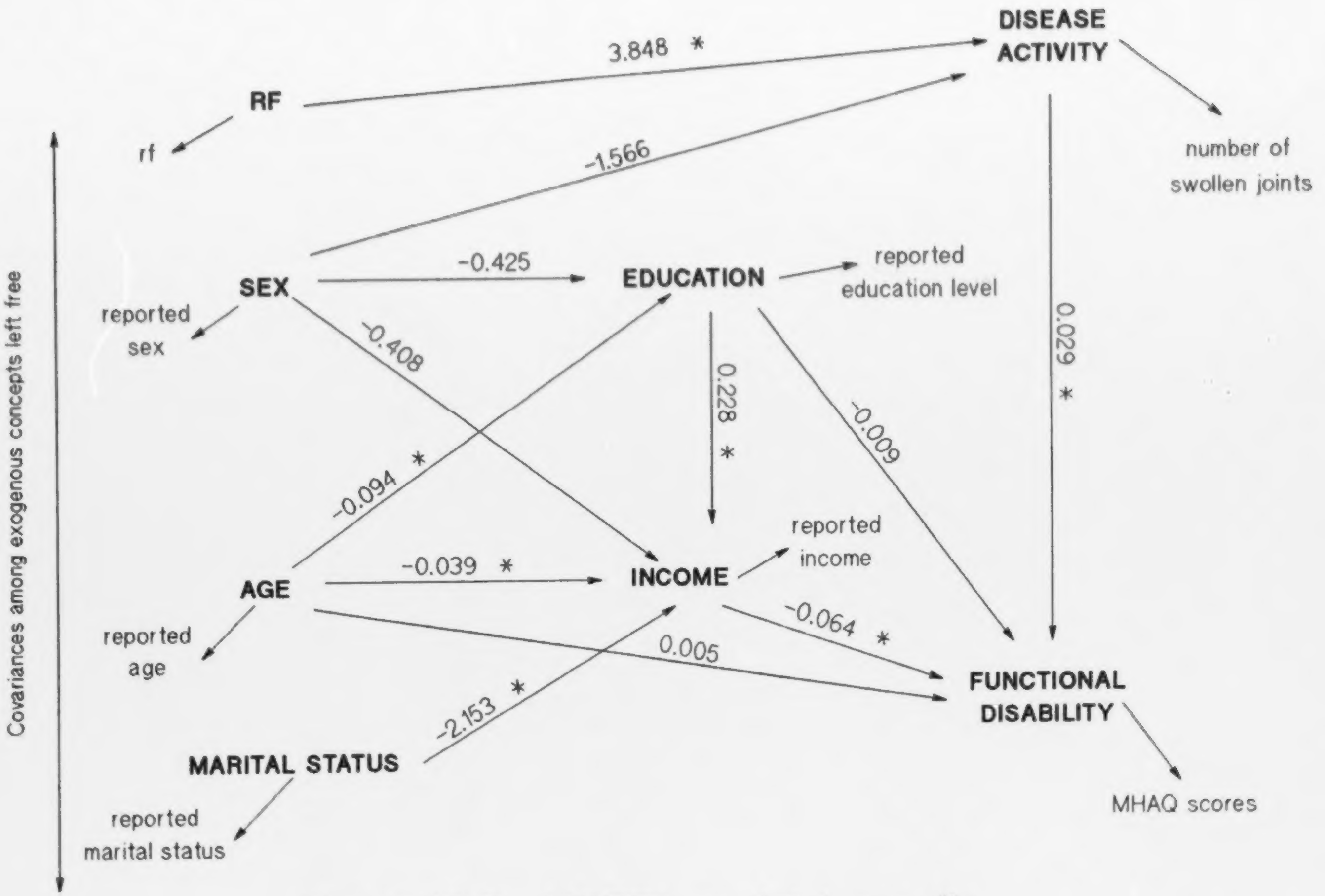

DISEASE ACTIVITY
number of swollen joints
RF
rf
3.848 *
-1.566
SEX
reported sex
-0.425
EDUCATION
reported education level
-0.408
0.228 *
-0.009
0.029 *
AGE
reported age
-0.094 *
-0.039 *
INCOME
reported income
-0.064 *
0.005
MARITAL STATUS
reported marital status
-2.153 *
FUNCTIONAL DISABILITY
MHAQ scores
Covariances among exogenous concepts left free

Figure 10.2. LISREL model 1, results

(* statistically significant coefficient, two-tailed $p<0.05$)

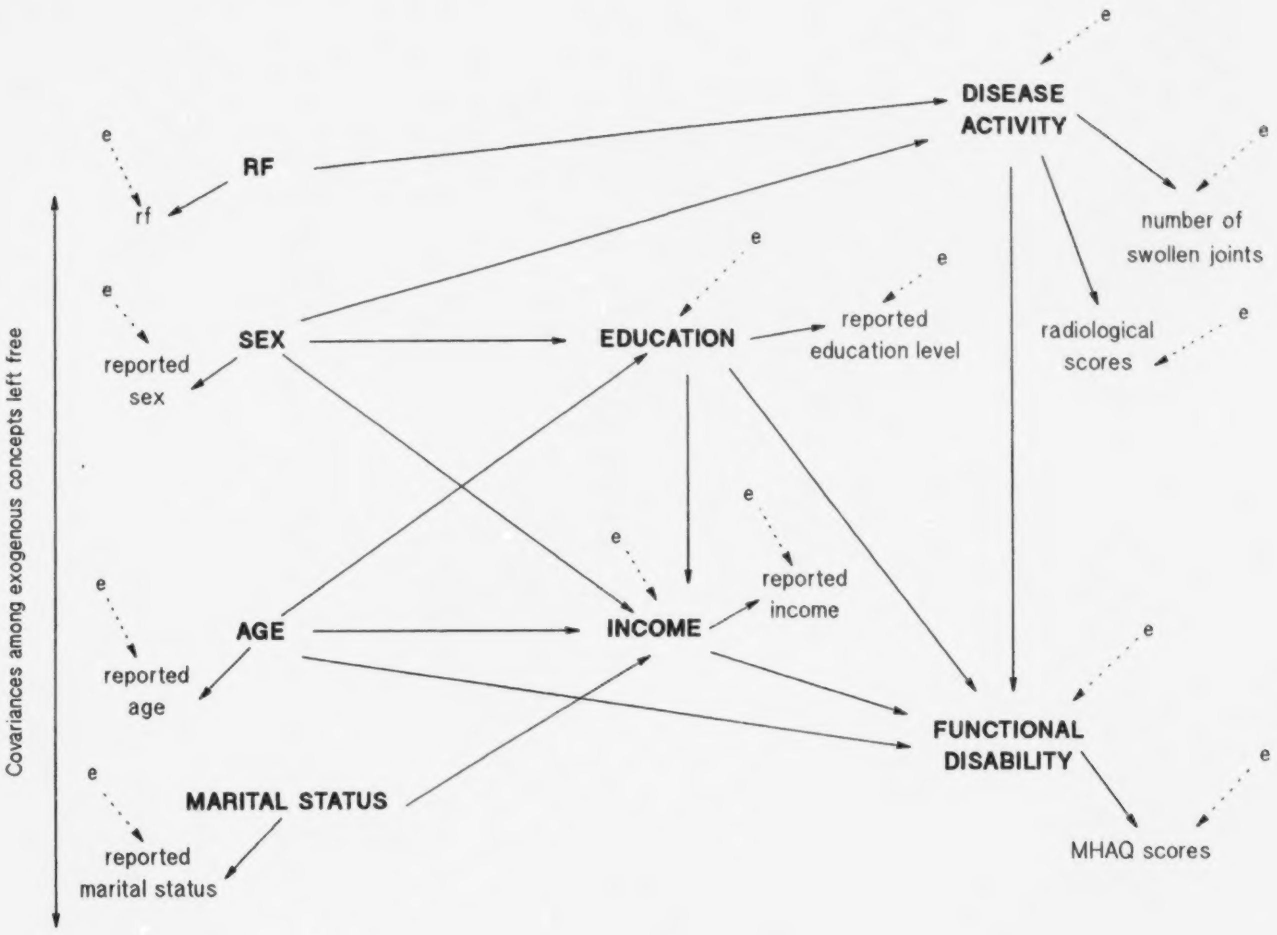

e
DISEASE ACTIVITY
e
RF
e
rf
number of swollen joints
e
e
e
reported sex
SEX
EDUCATION
reported education level
radiological scores
e
e
e
reported income
e
AGE
INCOME
reported age
e
FUNCTIONAL DISABILITY
e
e
MARITAL STATUS
reported marital status
MHAQ scores
Covariances among exogenous concepts left free

Figure 10.3. LISREL model 2

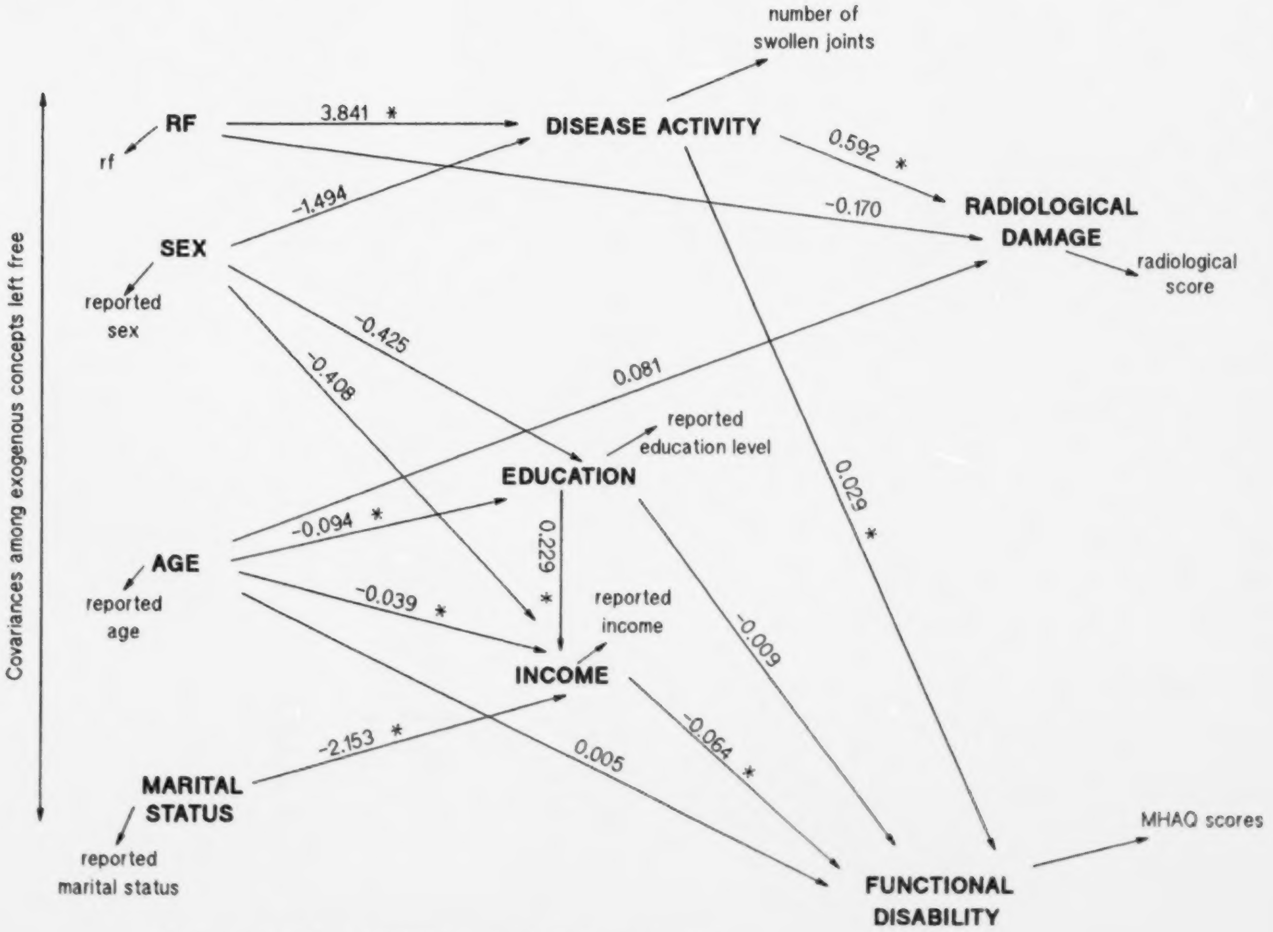

number of
swollen joints
RF
rf
3.841 *
DISEASE ACTIVITY
0.592 *
RADIOLOGICAL
DAMAGE
radiological
score
-1.494
-0.170
SEX
reported
sex
-0.425
-0.408
0.081
reported
education level
EDUCATION
0.029 *
-0.094 *
AGE
reported
age
0.229 *
-0.039 *
reported
income
INCOME
-0.009
-2.153 *
0.005
-0.064 *
MARITAL
STATUS
reported
marital status
MHAQ scores
FUNCTIONAL
DISABILITY
Covariances among exogenous concepts left free

Figure 10.4. LISREL model 3, results

(* statistically significant coefficient, two-tailed $p<0.05$)

CHAPTER 11

DISCUSSION AND CONCLUSIONS

1. DISCUSSION

The purpose of this study was to describe the clinical status and outcome of an inception cohort of patients with RA after 6-7 years of disease, and to try to establish if various clinical, therapeutic and social factors were associated with a variety of outcome measures.

The follow-up design was based on a cross-sectional survey and examination of a 1985 inception cohort of patients with RA, selected retrospectively. Although many studies of outcome in RA have been published, the majority are based on prevalent cases, and may be subject to selection bias. Furthermore, spurious associations through confounding variables may occur if the variables under study are related to the selection procedures. An inception cohort, based on incident cases, was necessary to determine the overall outcome of RA after a few years of disease. The mean duration of disease at the time of the study was 6.5 years. The majority of the previous studies are either long-term (>10 years) or of less than 3 years duration *(38, 62-64, 65, 76, 92, 123, 127, 156, 207-210, 211, 219, 220, 232, 233)*. It also has been suggested that it is between 5 and 10 years of disease that patients with RA will have their long-term prognosis defined *(225, 232)*.

The selection of 1985 incident cases was based on the diagnosis of RA by a rheumatologist. A potential concern was the proportion of patients that may never have consulted a rheumatologist. It is unlikely that this proportion was high, since a survey of general practitioners and internists suggested that the majority of new patients with RA are seen by a rheumatologist. The same survey showed that the proportion of patients in regular follow-up by rheumatologists is less, which indicates as well, the potential problems with prevalent surveys. An estimated 75% of the potential cohort cases participated in the study. This proportion would probably be larger if the denominator were based on 'true' 1985 RA. Since some of the patients assessed did not comply with the inclusion criteria, it is possible that some of the lost to follow-up individuals were either not RA, or had started their disease at a different point in time.

Patients who participated in the study were similar in demographic characteristics to non-participants. Although patients who had moved out of the study area were younger than those in the study cohort, when all the non-participants were pooled together, no significant age differences were observed.

In general, the characteristics of the cohort were comparable to the general descriptions of RA *(12, 132, 162)*. The female:male ratio was 2.3:1 and the mean age at onset was 52 years. These figures are similar to those included in most textbooks and reviews on RA, which indicates that no serious demographic biases occurred attributable to selection procedures.

1.1 OVERALL PROGNOSIS

The overall prognosis of the patients in the cohort appeared to be generally better than in some of the recently published studies *(191-194, 231, 283, 288)*. A high proportion of these patients (30%) had not developed erosions after 6 to 7 years of disease. This contrasts with some of the short-term studies where 80 to 90% of the patients have erosive disease 2 to 3 years after onset *(92, 156, 175)*. Although various procedures have been used in different studies to score radiological damage *(87, 136, 229)* it is unlikely that the differences in methods account for the variations in the findings. When reading techniques have been compared, similar results have been reported for the different methods *(87)*. It has been suggested that the rate of progression of the radiological damage is higher during the first 5 to 10 years of disease, stabilizing thereafter *(232)*. This may explain the increase observed in this study in the radiological score of patients with 7 years of disease as compared to those with 6 years. Other researchers have shown significant progression rates in only 6 months.

Approximately 40% of the patients had a chronic course and another 40% reported 'remissions'. Those patients with remittive disease had periods of time free of clinical synovitis, lasting 3 or more months, documented by a rheumatologist and confirmed by them. Although only 4 patients (3%) complied with the ARA criteria for remission *(187)* at the time of ascertainment, close to one third did not have clinical joint swelling on examination. It has been suggested that the remission criteria are too restrictive, with high specificity but low sensitivity. With less restrictive criteria, a larger proportion of patients may have been in remission at the time of the study. Short et al, in 1948, reported a remission rate of 17% in 250 patients receiving only simple medical and orthopedic measures *(233)*. Remission was defined there as inactive disease in asymptomatic patients with negative examination of the joints and normal or slightly elevated ESR. The remission rate in that report probably reflects the frequency of spontaneous remissions, since patients were 'untreated'. A study by Wolfe et al *(285)* documented a remission rate of 18%, using the ARA criteria, over a long period of time, in a large population of patients referred to private rheumatology clinics in the US. Since the study was based on patients coming to follow-up, this proportion was probably underestimated because of excess representation of patients with active disease. Moreover, this remission rate was similar to that observed in untreated patients which suggests that the sample was one of more severe RA patients, the criteria too restrictive, or that treatment is not related to remission.

A small percentage of the patients in this study (3%) had relatively typical palindromic arthritis *(218)*, but were included in the cohort because at least on one occasion the arthritis had lasted 6 weeks or more as documented by a rheumatologist. Of the overall proportion of patients with a palindromic start, most had developed a chronic course. These numbers, however, do not reflect any information on the rate of development of RA in palindromic arthritis, since patients had been selected with regard to a diagnosis of RA, and those with typical palindromic rheumatism, without long duration episodes had not been included in the study. Seventeen percent of the patients had a disease course that was classified as 'single flare'. These patients had a single flare of arthritis lasting 3 years or less and had remained in apparent remission since then. Although these patients may be part of the 'remittive group' it was thought best to consider them separately. There are suggestions that some of the patients with mild synovitis may in reality have a benign variant of RA, or perhaps a different disease. Some authors have made a distinction between RA and 'benign polyarthritis' or 'undifferentiated inflammatory polyarthritis' *(139, 287, 297)*. Wolfe et al *(287)* reported a lower prevalence of RF in these patients, and symptom and disease resolution after a variable period of time. These patients were somewhat similar to the patients labelled as 'single flare' in this cohort, who also had lower rates of RF although they did not reach statistical significance when compared to the other groups. Yet, since the relationship of this syndrome with RA is still controversial and all patients complied with the 1987 ARA criteria which are even more restrictive than the previous ones *(11, 37)*, it was decided to include them in the cohort.

As expected, patients with a chronic course had worse results for most disease activity variables tested, as well as for functional and radiological status.

The physical functional status of the patients in the cohort was reasonably adequate: all patients scored less than 2 in the MHAQ-ADL and 30% had normal ability for all the evaluated activities. In some recent studies, Pincus et al have reported severe functional impairment in patients followed at Vanderbilt University for 9 years

(191). These patients, however, had already a mean disease duration of 11 years at entry. Moreover, the duration of RA in these patients ranged from 2 to 32 years, suggesting that the sample was not homogeneous enough to generalize the conclusions. The Canadian study by Sherrer et al *(231)* also included patients at different stages in the course of the disease, with a mean duration at entry of 10 years. At the end of their study, after further 10 years, 17% of the patients had normal functional scores. Yet, more than half of the patients already had some degree of disability at entry. Both studies used the HAQ score to assess function but, because of the longer duration of disease and follow-up, they are not truly comparable to the 1985 inception cohort study reported here.

Several aspects may explain the relatively better prognosis of this cohort. First, the selection procedure in this study is closer to a community-based design than the majority of studies performed in single tertiary centers. It is well recognized that community or primary-care patients usually have milder disease. Furthermore, studies based on prevalent cases tend to select the more severe patients since they are followed-up more often. Another important aspect may be related to health care services utilization. Most patients in the 1985 cohort had been seen by a rheumatologist within the first 2 years of disease and had received remittive therapy early in the course of the disease. This contrasts with some of the available evidence from the US, where patients start gold therapy, on average, after 6 years *(30)*. Perhaps this relates to increased accessibility to medical services in Canada as opposed to the US.

1.2 THERAPY

The main purpose in evaluating therapy in these patients was to describe the use of different second-line drugs, and to determine if all rheumatologists treated patients similarly.

The first major aspect, already mentioned above, was the initiation of second-line therapy during the course of the disease. Most patients (85%) had received at least one drug, and the majority had started therapy within the first 2 years of disease. Sixty-one percent of the patients were receiving second-line drugs at the time of the study. The first drug of choice had been gold, most often parenteral, for the majority of patients. Yet, significant differences were observed among the different rheumatologists in the choice of second-line drugs. Some drugs were rarely or never used by some, and very often by others (e.g. auranofin). Differences in rheumatologists' practices have been shown for other aspects of patient follow-up *(111)*. A somewhat surprising finding was the use of combination therapy early in the course of the disease. Although scientific evidence as to the advantages of combining two or more second-line drugs is scarce, 18% of the patients had received combination therapy. A variety of different combinations had been prescribed. Sulfasalazine and antimalarials were administered in combination with another remittive drug approximately 40% of the time they were prescribed.

Withdrawal rates, from either toxicity or inefficacy were very high, as has been reported by many other observational studies *(78, 104, 243, 284)*. Although our sample size was too small to assess differences between some of the drugs, methotrexate was shown to have a lower termination rate. Wolfe et al reported a median time of 4.25 years for methotrexate compared to 2 years or less for intramuscular gold, auranofin, hydroxychloroquine or penicillamine *(284)*. Their results were markedly similar to those reported here. One of the major problems with the interpretation of these observational studies is related to the fact that some of the drugs are given later in the course of the disease than others, at a point in time when the disease may be less responsive to therapy. Therefore, the termination rates for inefficacy may be related more to the duration of disease of treated patients than to the potential effects of the drug. For example, in the study by Wolfe, patients starting auranofin had 6 years duration of disease compared to 10 years for patients on penicillamine. Although this particular study controlled for this and other factors in the analysis, others have not. In the 1985 cohort, not all patients had received the different drugs at the same point in time, but all of the drug therapies had started during the first 6 to 7 years.

Sulfasalazine had the highest withdrawal rates in this study, although the differences were significant only when compared to methotrexate. The sample size, however, was small and the statistical power was not adequate to detect differences among other drugs. The high withdrawal rates observed with sulfasalazine were mostly due to inefficacy. Situnayake et al *(243)*, found better results with the use of this drug. A potential confounder in this study may have been the order in which the different drugs were given, since the analysis was based on the number of therapies and not the number of patients. Since the sample size was small, adjustments for the number of previously received drugs by looking at even smaller subgroups would not yield meaningful results.

Several reports have highlighted the need to assess long-term therapy in RA through observational studies. In general, short-term controlled clinical trials have shown a beneficial response for most of the drugs currently in use. Effectiveness in the long-term appears to be a different matter, with high withdrawal rates *(198)*. A major concern, among others, with the observational studies is the confounding effect of severity of the disease. If no beneficial response is observed in a treated group compared to untreated patients, it may be because the treated patients were more severe and received therapy for that reason. Some differences were observed in the disease activity variables between treated and untreated patients, and in relation to duration of therapy when all patients and all drugs were included in the analysis. This suggests that patients taking second-line drugs were more severe to start with. Radiological scores however were similar for both groups of patients. To decrease the potential confounder effect of severity, patients then were analyzed on an 'intent to treat' basis. Only those patients who had started therapy were included. When all the different drugs were considered together, no significant differences were observed in the outcome variables according to length of therapy.

The subgroup of 70 patients who had received GSTM showed different results. In these patients, duration of therapy was significantly associated with lower joint counts and radiological scores. Epstein et al *(71, 72)* reported no improvement in the long-term functional status of patients treated with gold salts. Some of the methodological aspects of these results were subject to further controversy, partly because of the observational nature of the design. Others have reported an increase in survival in patients treated with gold *(143, 158)*. Although a significant association was found in this study with length of therapy and a variety of clinical parameters, no relationship was observed with functional status. Although the sample size was not sufficiently large to detect small correlations, any association, if present, would be smaller than for other outcome measures. An interesting finding was the difference in radiological scores between those treated for a year or less and those treated longer. Evidence for the potential effect of gold on the erosion rates was initially presented by Sigler *(237)*. Yet, the issue remains controversial. There is general agreement that remittive therapy does not normally reverse radiological damage, but it may slow the rate of erosions, in particular in those patients with a clear beneficial clinical response

(119, 132). This would be in accordance with the findings in this study, where those patients who continued to receive the drug (and in all probability were having some clinical response) had less damage. Because this is an observational study, it also could be argued that those patients continuing gold therapy were just experiencing spontaneous remissions or fluctuations, wrongly attributed to gold. This point can not be completely dismissed, yet, the majority of patients that withdrew from gold therapy did so because of toxicity as opposed to inefficacy, and a similar rate of spontaneous remissions and milder disease should be expected in these patients.

To assess the overall therapeutic interventions in the cohort, part of the questionnaire was related to use of other drugs and health services utilization. Most patients had seen a rheumatologist within the first 2 years of disease, and the majority remained in follow-up by that same physician. Visits averaged 2 per year.

Steroid use was low, with 16% of the patients ever having received glucocorticoids for therapy of RA. Intraarticular and soft tissue injections had been frequently administered.

Twenty percent of the patients had surgical procedures in joint and tendon structures, but not always related to RA. The most common procedure was carpal tunnel release.

Although the majority of patients had received physical therapy and over a third had attended a patient education program, only 23% reported that they regularly performed therapeutic exercises. This also has been reported previously *(176)*, and it would appear that patients lose interest as time goes by.

Approximately one fifth of the patients had used some form of homeopathic or herbal therapy. In general, these patients appeared to be younger, better educated and reported higher incomes.

1.3 DETERMINANTS OF CLINICAL STATUS AND OUTCOME

Onset of disease was related to the eventual course of the disease; patients with gradual onset developed chronicity more often than the rest. This association, however, was small, and when the outcome measures were analyzed in relation to the type of onset, no significant differences were observed for patients in the 3 groups.

No major differences were observed between DR4 positive and negative patients for the various outcome measures. It is still controversial whether DR4 is related to severity or susceptibility *(40, 100, 101, 103, 126, 182, 241, 250, 269, 273, 276, 295)*. Although only 87 patients were typed for DR4, they were similar in characteristics to those who had not been typed, and it is unlikely that selection bias may have affected the results. Another aspect is the size of the sample, and its statistical power to detect differences. Other studies reporting differences, however, have been conducted in smaller samples. One plausible explanation relates to the finding that only some of the specific sequences in the third hypervariable region of the ß chain of the DR4 molecule relate to disease *(58, 200, 279, 292)*. Since the frequency of this sequence varies among different DR4 sub-populations *(292)*, it is likely that some of the DR4 patients in the study did not possess the described susceptibility allele and, in addition, it may have been present in non-DR4 individuals. To date, typing for the third hypervariable region has not been performed in these patients.

The associations of the different outcome indices with various factors varied according to the measure under consideration. This was shown at the bivariate analysis stage and with the 3 multivariate analysis methods (multiple linear regression, multiple logistic regression and LISREL). The purpose of using multiple regression methods was to study the linear relationships of different determinants with the clinical status of patients, by adjusting for the effect of confounders. These models assume direct one-way relationships (or effects) with the dependent variables. Logistic regression methods were used to dichotomize the outcome variables into 'mild' and 'severe' according to predetermined cut points. This was particularly important because the dependent variables, in general, had distributions skewed to the right, with a large proportion of patients having normal values. Another advantage of this method was the estimation of odd ratios which are generally better visualized and interpreted by clinicians.

The results of these analyses suggested some indirect associations. Rheumatoid factors, for example, were associated in bivariate analysis with both disease activity and radiological damage, but when disease activity was entered in models with the radiological score as the dependent variable, the association with RF was decreased. These results suggested that the effect of RF on radiological damage was exerted through disease activity, which is consistent with clinical judgement.

To study these indirect effects, as well as others, modelling with LISREL methods was undertaken. Only some variables were included in the LISREL models, primarily to study a relatively simple model. The variables selected were those thought to have most relevance from the available evidence in the literature and the previous regression analyses in this data set. The number of swollen joints was chosen as the indicator of disease activity. Although the other joint indices (number of tender and limited joints) had higher significant associations with functional status, indices including joint swelling are more widely used clinically as parameters of disease activity, and have better face validity, and probably construct validity as well (Table 6.16).

LISREL models allow for controlling of confounders as well as for including direct and indirect effects. Moreover, a measure of the reliability of the indicator can be incorporated by defining the proportion of variance in the indicator thought to be due to measurement error. The models analyzed appeared to fit adequately with the data set. There was no indication from the different indices provided by LISREL (modification indices and partial derivatives) that including a new effect, would significantly increase the fit of the model. In general, the results from all 3 multivariate methods were consistent in several aspects.

Outcome in RA appears to be fairly complex, with different dimensions relating to various aspects of the disease. In general, it would appear that radiological damage and functional status are unrelated outcomes at this point in the course of the disease, and that any relationship would be spurious, given by the effects of disease activity on both variables. This lack of association between X-ray changes and function also has been described by others *(65, 190, 212)*, but not all *(209)*. It is likely that radiological damage may affect functional outcome at a later stage in the course of RA.

Different determinants were associated with the various outcome variables. Disease activity could be considered a primarily 'biological' variable related to the presence of nodules, rheumatoid factors and female sex. Radiological damage also was predominantly associated with 'biological' factors, such as a history of nodules, RF and disease activity, with RF exerting its effect through disease activity. In all multivariate models, the presence of nodules had a stronger effect than RF. In some models, in order for the RF to show an association with outcome measures, the variable 'nodules' had to be removed, but in others both showed significant independent effects. This suggests that both the presence of nodules and seropositivity are related to severity of the disease, but that in general, although nodules and RF are strongly associated, the presence of nodules has a stronger component related to severity. This was consistent, even though some patients with nodules were seronegative. In general, it is accepted that RF has a direct pathogenetic effect on both the occurrence of nodules and the disease activity. The findings in this study suggest that there is an effect, bound to the 'marker' or 'indicator' nodules that relates to severity of disease, and is independent of seropositivity for RF. This is not unlikely, since only a proportion of seropositive patients will ever develop nodular disease. Rheumatoid nodules have been associated with poor prognosis in several reports *(46, 63, 160, 205, 207, 225)*.

Physical disability, had a 'biological' component as well, demonstrated by the association with disease activity variables, in particular joint indices. A strong association was observed for the number of tender joints and the number of limited joints. A significant association with socioeconomic status also was found. Total household income was related to function, with patients in the lower income classes having more disability. A variety of factors could explain this association. First, the results could be biased by using a variable (MHAQ-ADL) that is too subjective and does not really represent 'true' functional status. There is strong evidence, however, that this self-response index is highly reliable and valid and has high correlations with all the objective measures of functional capacity *(190, 195)*. Moreover, in this study, the MHAQ-ADL was associated with other measures such as number of limited joints and indices of disease activity which suggests that the index is valid. A potential confounding and biasing factor could have been age, not only for its effect on function, but also because older individuals may report less than the real earned income (only reporting pensions and not other sources of income). The results, however, were controlled for age, and the association with income was independent of this factor.

Another important consideration is the direction of the cause-effect relationship. It could be argued that patients with more disability earn less income. This effect nevertheless, would be only partial, since the variable used was total household income as opposed to personal income. Although there were differences in the employment status of patients with low vs high income (17% full-time employed in the low group vs 41% in the high income group), the largest difference was observed for retirement (52% of the low income vs 17% of the high income group). The number of patients receiving government disability benefits was similar and low in both groups (4% vs 2%). Furthermore, more women in the high income group stayed at home, and did not work at all (24% vs 8% in the low income group). These findings were consistent with the relationship of age with income which showed a statistically significant correlation. Yet, as mentioned before, the association of income with disability remained significant after adjusting for age in the different models. This adjustment would not control entirely for a biased reporting in the elderly. However, when only the 81 patients 65 years and younger were included, the correlation between MHAQ and income remained significant (-0.39, $p<0.001$), although the relationship with other variables such as joint indices was no longer statistically significant.

Several researchers have investigated the role of education on the outcome of RA. Pincus and Callahan have consistently found a relationship between lower education levels and functional outcome and mortality after adjusting for other covariates *(41, 189)*. The effect of income was not established in these studies. Because of the strong association between education and income, we repeated some of the regression models excluding the effect of income. Education level did not achieve two-tailed statistical significance; however, our sample was smaller than the samples studied by Pincus, and statistical power may have been insufficient. The association, however, was in the 'right' direction, and was significant for the unadjusted bivariate association with lower education levels related to disability. This effect of education also has been confirmed by other investigators in the US *(144, 146)*; yet, a recent Canadian study found no relationship betwee education and clincal status *(275)*.

A few studies have looked at income from a different perspective and have found results consistent with the observations in this cohort. Meenan et al *(166)* found a significant association between premorbid income and subsequent work disability in patients with RA. Leigh et al *(146)* also found an association between income and disability after controlling for education. These studies, however, were based on prevalent cases, and may be subject to the confounding effect of referral or attendance patterns: patients with lower incomes may only attend the clinics for follow-up (and therefore be selected for the studies) when their disease becomes severe and disabling. This study was based on the follow-up of an inception cohort, and was less susceptible to this particular bias.

It is unclear how these socioeconomic variables affect the functional status of RA. Whether these patients are less compliant with therapy is unknown. In this study, patients with lower incomes did not seek rheumatologists' services or start remittive therapy at later stages than those with higher incomes. On the contrary, the findings were reversed, with patients in the lower brackets seeking medical attention and starting drug therapy earlier than the rest. The effects of specific occupations were not investigated here. It is possible that low income acts as a surrogate for some occupations that may be detrimental to the functional status of patients with arthritis. Meenan et al *(169)*, nevertheless, did not find a significant association between work disability and occupation (manager, sales vs service, labour). The relationships between the different occupations, income and disability remain unclear, but may play an important role in determining why the socioeconomic status of patients is at least as important as biological factors in the functional outcome of these patients.

Another theoretical view has been based on the suggestion that patients in the lower socioeconomic status may have decreased 'self-efficacy' and increased 'learned-helplessness' which eventually may contribute, through yet unknown mechanisms, to poor outcome. It has been suggested that patients with low 'self-efficacy' do not have the ability to control those aspects of the disease that can be controlled, and that their psychological distress is increased *(33, 42, 152)*. The causal inferences for these variables are very difficult to determine since the direction of the cause-effect of these associations would have to be established with measures of these indices before any outcome (or even the disease) occurs.

2. CONCLUSIONS

This study described and analyzed the clinical status and outcome of patients with RA after 6.5 yeras of disease. Some of the findings may be subject to the common problems of observational studies but, the fact that this study was conducted on a true inception cohort decreases the probability of selection bias as compared to other published outcome studies.

The findings can be summarized as follows:

1. In general, the prognosis for RA after 6.5 years of disease was good, with significant proportions of patients within the normal ranges for different outcome measures. Thirty percent of these patients had normal X-rays at this stage.

2. Second-line drugs were administered to these patients early in the course of the disease. Nevertheless, withdrawal rates were high for most drugs. The discontinuation rates were highest for sulfasalazine and lowest for methotrexate.

3. Duration of GSTM therapy in those patients that ever started this treatment was associated with a better outcome for most measures, including radiological scores. This finding suggests that parenteral gold has a beneficial effect in those patients that are able to continue the therapy.

4. Disease activity, radiological damage and physical functional status represent different aspects of the overall clinical status of patients with RA and have different associations.

5. Variables associated with increased disease activity were the presence of rheumatoid nodules, seropositivity for RF and female sex.

6. The major determinants of radiological damage were disease duration and disease activity as measured by the number of swollen joints. Rheumatoid factors were associated with radiological damage mainly through the increase in disease activity.

7. Physical disability was strongly associated with parameters of disease activity and with total household income. No significant associations were observed with RF and radiological scores.

8. The results from the various multivariate analyses suggest that different dimensions define the clinical status of patients with RA at this stage in the course of the disease. The first one relates to articular damage and the second to functional status. Disease activity is significantly related to both of these outcomes. Sociological variables, in particular income, appear to be significantly associated with disability, with patients in the lower economic levels having decreased functional status. This finding, supported by United States studies, was a surprise in light of Canada's universal health care system.

3. RECOMMENDATIONS FOR FUTURE RESEARCH

The following recommendations for future research are based on the findings of this study.

1. This report was based on a inception cohort with a mean duration of disease of 6.5 years. Most of the longer follow-up studies are based on prevalent cases. It is therefore important to determine if the findings of this study are also present at a later point in the course of RA. Long-term inception cohort studies are necessary to determine overall prognosis at later stages, without the bias and confounding effects of a cross-sectional selection of patients. Further assessments of this cohort will be conducted in following years.

2. A major finding in this study was the potential relation of socioeconomic status to functional outcome. The role of sociological factors in the outcome of RA needs to be explored further. While it is clear that the association exists, it is also likely that these variables stand as surrogates for other factors. The relationships of socioeconomic status to health utilization, compliance with therapy and potential deleterious effects of various occupations in the context of RA were not objectives at this time. Future studies should focus on these issues.

3. The effect of radiological damage on functional status was very small and did not reach statistical significance when controlling for other variables. Yet, the patients in this study had a mean duration of disease of 6.5 years. It is possible that radiological damage may play a significant role in the development of disability at later stages in the course of the disease. Long-term cohort studies should clarify this issue.

4. The majority of patients in this cohort had been treated very early in the course of the disease. The overall outcome was better than the reported outcome in many recent

publications. Longer duration of therapy with parenteral gold was associated with a better outcome in patients treated with this drug. These findings indirectly suggest that early remittive therapy and long-term therapy with gold salts improve outcome in RA. Because of the difficulties and ethical considerations in conducting long-term controlled clinical trials, it is recommended that observational studies be designed and conducted to address the long-term effects of second-line therapy in patients with early rheumatoid disease.

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APPENDIX 1

LETTER TO PATIENTS

Rheumatic Disease Unit

562 Heritage Medical Research Center
University of Alberta
Edmonton, Alberta
T6G 2S2
(403) 492-6296

Rheumatoid arthritis is a disease of long duration and unknown cause. The majority of people with RA will experience arthritis for several years with varying degrees of severity and disability. It is unclear why some patients experience disease remissions while others experience continuing joint problems. The University of Alberta is conducting a study to determine which factors may be responsible for the differences in severity among patients. The factors under study include age, socioeconomic characteristics and previous therapies. We are contacting a large number of patients with arthritis to ask them to participate in the study. Your name and address was provided to me by your rheumatologist, who allowed me to contact you, in order to explain you the objectives and characteristics of the study.

All assessments will be conducted by myself at a single visit at the University. The assessment will consist of: 1) interview and medical history, 2) physical examination, 3) self-response questionnaire, 4) hands X-ray and 5) blood test (CBC, rheumatoid factors). These tests are part of routine medical care of patients with arthritis, to determine whether the disease has remained stable or progressed and will not be repeated if they have been done in the previous 6 months.

All information recorded will be confidential and at no time will your name be used. Any pertinent information or results will be forwarded to your physician upon request. You will also be able to contact me in regard to the results of the tests.

Participation in the study is voluntary. Refusal to participate will in no way affect your medical care. If you are interested in this assessment, please phone 492-6296 to ask for an appointment. If you have any questions, please do not hesitate to contact me at this same phone number.

Thank you for your attention to this matter.

Dr Maria Bruera

APPENDIX 2

AMERICAN RHEUMATISM ASSOCIATION CRITERIA FOR THE DIAGNOSIS OF RHEUMATOID ARTHRITIS

THE 1987 REVISED CRITERIA FOR THE CLASSIFICATION OF RHEUMATOID ARTHRITIS (TRADITIONAL FORMAT)*

1. MORNING STIFFNESS: Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.

2. ARTHRITIS OF 3 OR MORE JOINT AREAS: At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.

3. ARTHRITIS OF HAND JOINTS: At least 1 area swollen(as defined above) in a wrist, MCP, or PIP joint.

4. SYMMETRIC ARTHRITIS: Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).

5. RHEUMATOID NODULES: Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician

6. SERUM RHEUMATOID FACTOR: Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control subjects.

7. RADIOGRAPHIC CHANGES: Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

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* For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 of these criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis s not to be made.

APPENDIX 3

PHYSICIAN SURVEY FORM

August 1992

University of Alberta

Dear Dr

The Rheumatic Disease Unit at the University of Alberta is currently conducting a clinical study on the outcome of patients with rheumatoid arthritis. As part of this study we want to estimate the approximate incidence and prevalence of rheumatoid arthritis in metropolitan Edmonton. All the rheumatologists in the city have participated in the study by allowing us to collect data from their records. This protocol was approved by the Ethics Approval Committee of the Faculty of Medicine. In order to adjust our results it is necessary for us to have an approximate idea of how many patients with rheumatoid arthritis never see a rheumatologist. We have selected a random sample of 160 physicians to whom we are mailing this questionaire. We would greatly appreciate it if you could mail the questionnaire to us using the enclosed, stamped, self-addressed enveloppe. All the information in the questionnaire is confidential. As you can see there is no personal ID number that can link a given questionnaire to an individual physician. For this reason, it is important that we receive as many questionnaires as possible since we will not be able to contact again the non-respondants.

Please answer the following questions to the best of your knowledge and feel free to add any information that you may consider useful to us.

1. How would you best define your practice?

   1. General Practice _____
   2. Family Practice _____
   3. Internal Medicine _____
   4. Retired or not currently in practice _____
   5. Other _____

please specify ______________________________

2. How often do you see patients with rheumatoid arthritis as part of your practice?

   1. Never _____
   2. Rarely _____
   3. Sometimes _____
   4. Often _____

3. When you see a patient who you think has rheumatoid arthritis and who has never seen a rheumatologist before, how often do you request a consult, at some point during the disease course, from ANY of the rheumatologists in the city? (we realise the difficulties in quantifying your answer; however, a crude approximation will be sufficient)

1. More than 90% of the time ____
2. 70-90% of the time ____
3. 50-70% of the time ____
4. Less than 50% of the time ____
5. Not applicable ____

4. What percentage of your patients with rheumatoid arthritis are regularly followed by a rheumatologist (≥ once a year)? (Again, only a crude approximation is required)

1. 90% or more ____
2. 70-90% ____
3. 50-70% ____
4. Less than 50% ____
5. Not applicable ____

5. In order to better analyze our results we would like to have some demographic characteristics of the physicians responding to this questionnaire. We would greatly appreciate it if you could complete the following data.

1. Year of birth ____

2. Gender
   male ____
   female ____

3. Year of graduation ____
   (from medical school)

Thank you for taking time to answer this questionnaire. Please feel free to add any pertinent comments.

COMMENTS

APPENDIX 4

MEDICAL CHART REVIEW FORM

INCLUSION FORM

LAST NAME: FIRST NAME:

AHC: RHEUMATOLOGIST:

DOB: AGE: SEX:

ADDRESS: CITY: P CODE:

PHONE NO (H): PHONE NO (W):

FAMILY DR:

OTHER RHEUMATOLOGISTS SEEN:

Dr 1st SEEN: LAST SEEN:

ONSET: DEFINITE 1985______
PROBABLE 1985______
UNKNOWN____________

TYPE OF ONSET: acute gradual palindromic unknown

		NOT AVAILABLE
1) MS > 1 HOUR	________________	________
2) SWELLING $\geq$3 JOINT AREAS	______	________
3) SWELLING PIP,MCP OR WRIST	____	________
4) SYMMETRICAL SWELLING	________	________
5) NODULES	__________________	________
6) RF	______________________	________
7) RADIOGRAPHS: erosions	_________	________
space narrowing	_______	________

LETTER 1: PHONED:
LETTER 2:
PT RESPONSE: assessed
deceased
refuses to participate
moved ot
lost to follow-up

MEDICAL CHART ABSTRACT FORM

CASE NO:

LAST NAME:

FIRST NAME:

	1985	1986	1987	1988	1989	1990	1991
RHEUMATOL							
TIMES SEEN							
HOSPITALIZATONS EDUCATION PROGRAM							
ACTIVITY (active/inact)							
No JOINTS (Poly/oligo)							
ACTIVE JTS							
DRUGS							
SIDE EFFECTS							

LAB AND X-RAYS

	1985	1986	1987	1988	1989	1990	1991
HB							
WBC							
PLATELETS							
ESR							
RF							
ANA							
OTHER							
HANDS X-RAY							
EXTRAARTICULAR							
COMMENTS							

MEDICATION CHART

DRUG	No Times*	M/Yr begun	M/Yr dc	Taking now	No months taken	Side Effects**	D/C+				Response			
							SE	LE	NLN	By PT	no	weak	good	excellent
Chloroquine														
Auranofin														
IM Gold														
Methotrexate oral__IM__														
Penicillamine														
Corticost.														
Azathioprine														
Salazopyrin														
Other														

* 0=never, if taken 1 or more list

** 0=no, if yes specify

+ SE=side effect, LE=lack of effect, NLN:no longer needed

APPENDIX 5

PERSONAL INTERVIEW FORM

DATE SEEN: CASE NO:

LAST NAME: FIRST NAME:

INCLUSION: pt phoned after receiving letter: contacted by phone:

AHC:

ADDRESS:

PHONE (h): PHONE (w):

DOB: AGE: SEX: M F

ETHNIC ORIGIN: W B O N H other:

OCCUPATION:

FAMILY DR:

CURRENT RHEUMATOLOGIST:

AGE AT ONSET:

ONSET 1985: definite probable

Month/Season:

DURATION DISEASE: AGE AT ONSET:

TYPE OF ONSET: gradual____

acute______

palindromic_____

OCCUPATION AT ONSET:

In previous 6 months before disease started:

PREGNANCY____ ABORTION_____

SICKNESS_____ IF YES, SPECIFY__________________________________

No RHEUMATOLOGISTS SEEN:

SEEN BY RHEUMATOLOGIST:

1985:	Dr________
1986:	Dr________
1987:	Dr________
1988:	Dr________
1989:	Dr________
1990:	Dr________
1991:	Dr________
1992:	Dr________

VISITS TO FAMILY DOCTOR________ per year

PRIVATE INSURANCE: YES_____ NO_____ IF YES, SINCE______

% COST OF DRUGS COVERED BY INSURANCE:______%

PAST MEDICAL HISTORY AND SURGERIES

SURGERIES

ADMISSIONS (specify if RA related)

COMORBIDITY				COMMENTS
HYPERTENSION	YES	NO	YEAR_____	
CHD-ANGINA	YES	NO	YEAR_____	
MYOCARDIAL INFARCTION	YES	NO	YEAR_____	
STROKE	YES	NO	YEAR_____	
DIABETES MELLITUS	YES	NO	YEAR_____	
CHRONIC BRONCHITIS	YES	NO	YEAR_____	
CANCER	YES	NO	YEAR_____	
PEPTIC ULCER	YES	NO	YEAR_____	
RENAL DISEASE	YES	NO	YEAR_____	
PSYCHIATRIC DISEASE	YES	NO	YEAR_____	
THYROID DISEASE	YES	NO	YEAR_____	
OTHER				

EXTRA-ARTICULAR DISEASE			
NODULES	YES	NO	YEAR_____
RAYNAUD'S	YES	NO	YEAR_____
DRY MOUTH	YES	NO	YEAR_____
PERICARDITIS	YES	NO	YEAR_____
FELTY'S	YES	NO	YEAR_____
VASCULITIS	YES	NO	YEAR_____
EPISCLERITIS	YES	NO	YEAR_____
PSORIASIS	YES	NO	YEAR_____

FAMILY HISTORY:

RA:

PSORIASIS:

OTHER RHEUMATIC DISEASES:

GENERATIONS ALIVE: grandparents parents siblings children >20 yrs

ETHNIC BACKGROUND: MATERNAL____________________

PATERNAL____________________

PREGNANCIES:

DELIVERIES (DOB children): LACTATION (duration):

MENOPAUSE yes_____ no_____ age at menopause:______ year of menopause: _____

ESTROGEN REPLACEMENT THERAPY: FROM______ TO______

TYPE and DOSE:_____________

CONTRACEPTIVE USE SINCE 1984 (No months):

Before 1984:

1984-

1985-

1986-

1987-

1988-

1989-

1990-

1991-

REMISSIONS (> 2 months with no swelling) YES___ NO___

No REMISSIONS:

DATE OF REMISSIONS DRUGS AT TIME OF REMISSION

COURSE: progressive____

chronic with superimposed flares____

remittive____ no flares:____ duration flares:____

palindromic w/1 or more episodes >6 wks____ no episodes/yr:____

single flare (>6wk) and remission now____ duration flare:____

EDUCATION PROGRAM: yes____ no____ DATE:

GLENROSE ____ U of A ____ RAH_____ Other_____

PHYSIOTHERAPY: 1985 1989
1986 1990
1987 1991
1988

never____

ACTIVE THERAPEUTIC EXERCISE (taught by therapist or educ program):

never____ 1985 1986 1987 1988 1989 1990 1991

>3/wk____ 1-3/wk____ <1/wk____ never____

USE OF ORTHOTICS

PRESCRIBED: splints____ braces____ shoe inserts____(soles, pads) collar____

Types of orthotics used:

Type	Currently using	Very useful	Somehow useful	Not useful

RECREATIONAL EXERCISE OR SPORTS: yes____ no____

type_____________ min/session____ since______ >3/wk___ 1-3/wk___ <1/wk___

type_____________ min/session____ since______ >3/wk___ 1-3/wk___ <1/wk___

type_____________ min/session____ since______ >3/wk___ 1-3/wk___ <1/wk___

EXERCISE ≥3/WK DURING 5 YRS PRIOR TO RA yes_____ no_____type_________

SURGERY FOR RA

TYPE	DATE	REMARKS

CURRENT MEDICATIONS:

SELF-MEDICATIONS (ALTERNATIVE MEDICINE): DATE

Herbs

Chiropractor

Acupuncture

Other

VITAMINS DATE

CORTICOID INJECTIONS:

site: times:

RADIOCHEMICAL SYNOVECTOMY:

OTHER:

MORNING STIFFNESS:__________ MINUTES

PAIN SCALE: NO PAIN └──────────────────────────────┘ MOST PAIN

HEIGHT______ WEIGHT______ DOMINANT HAND: left right

RA CRITERIA (No):

1) MS >1 HOUR_______

2) SWELLING $\geq$3 JOINTS______specify______________________________

3) SWELLING PIP, MCP OR WRIST_______

4) SYMMETRICAL SWELLING_______

5) NODULES_______

6) RF_______

7) RADIOGRAPHS:erosions__________

space narrowing______ j-a osteopenia_______

JOINT EXAMINATION

CERVICAL PAIN______ ROM______

	RIGHT			LEFT		
	PAIN	SWELLING	ROM	PAIN	SWELLING	ROM
SHOULDER	____	____	____	____	____	____
ELBOW	____	____	____	____	____	____
WRIST	____	____	____	____	____	____
MCP 1	____	____	____	____	____	____
MCP 2	____	____	____	____	____	____
MCP 3	____	____	____	____	____	____
MCP 4	____	____	____	____	____	____
MCP 5	____	____	____	____	____	____
IP 1	____	____	____	____	____	____
PIP 2	____	____	____	____	____	____
PIP 3	____	____	____	____	____	____
PIP 4	____	____	____	____	____	____
PIP 5	____	____	____	____	____	____
FIST			____			____
HIP	____		____	____		____
KNEE	____	____	____	____	____	____
ANKLE	____	____	____	____	____	____
MTP	____			____		

DEFORMITIES: Hands: Ulnar dev____ MCP s-l____ swan neck____ boutonniere____
(R, L, Bil) Feet: hallus valgus____ claw toes____

PAIN: pain on motion or tenderness
0 = none
1 = minimal (on questioning)
2 = moderate (spontaneous response)
3 = severe (withdrawal)

SWELLING:
0 = none
1 = mild (synovial thickening without loss of bone contour)
2 = moderate (loss of bone contours)
3 = severe (bulging synovial prolif. with cystic characteristics)

ROM: (range of motion)
0 = normal
1 = restricted, ≥ 50% normal range
2 = restricted, < 50%

MEDICATION CHART

DRUG	No Times*	M/Yr begun	M/Yr dc	Taking now	No months taken	Side Effects**	D/C+				Response			
							SE	LE	NLN	By PT	no	weak	good	excellent
Chloroquine														
Auranofin														
IM Gold														
Methotrexate oral___IM___														
Penicillamine														
Corticost.														
Azathioprine														
Salazopyrin														
Other														

* 0=never, if taken 1 or more list

** 0=no, if yes specify

+ SE=side effect, LE=lack of effect, NLN:no longer needed

APPENDIX 6

SELF-RESPONSE QUESTIONNAIRE

SELF-REPORT QUESTIONNAIRE CASE NO

The questions below concern your personal characteristics, lifestyle and daily activities. Please try to answer each question, even if you do not think it is related to you or any condition you may have. There are no right or wrong answers. Please answer exactly as you think or feel. All answers are confidential. Analysis of the data will be performed using case numbers and at no time will your name be used.

Today's date (day/month/year):____________ Time:_________ am pm

1. Date of Birth:

2. Place of birth (province and country):

3. How long have you lived in Edmonton?:

Always____ For the past______years

4. Please check the ONE best answer for your abilities.

AT THIS MOMENT, are you able to:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
a) Dress yourself including tying shoelaces and doing buttons?	______	______	______	______
b) Get in and out of bed?	______	______	______	______
c) Lift a full cup or glass to your mouth?	______	______	______	______
d) Walk outdoors on flat ground?	______	______	______	______
e) Wash and dry your entire body?	______	______	______	______
f) Bend down to pick up clothing from the floor?	______	______	______	______
g) Turn regular faucets on and off?	______	______	______	______
h) Get in and out of a car?	______	______	______	______

5. Have you changed your lifestyle and/or everyday activities because of your arthritis?

yes_____

no _____

If you answered yes, which of the following statements reflect some of these changes

1. I don't work anymore because of my arthritis	YES	NO
2. I have changed occupations because of my arthritis	YES	NO
3. I work less hours/wk because of my arthritis	YES	NO
4. I socialize less with friends because of my arthritis	YES	NO
5. My arthritis has damaged my family relationships	YES	NO
6. My income has decreased because of my arthritis	YES	NO

6. This section is concerned with your attitudes towards how you see yourself dealing with your condition. Each item is a belief with which you may : 1) STRONGLY DISAGREE, 2) DISAGREE, 3) DO NOT AGREE OR DISAGREE, 4) AGREE, or 5) STRONGLY AGREE. Circle the number beside each statement that best describes how you feel about the statement. Since these questions are a measure of your personal beliefs, there are no right or wrong answers.

	STRONGLY DISAGREE	DISAGREE	DO NOT AGREE OR DISAGREE	AGREE	STRONGLY AGREE
1.My condition is controlling my life	1	2	3	4	5
2.Managing my condition is largely my own responsability	1	2	3	4	5
3.I can reduce my pain by staying calm and relaxed	1	2	3	4	5
4.Too often, my pain just seems to hit me from out of the blue	1	2	3	4	5
5.If I do all the right things, I can succesfully manage my condition	1	2	3	4	5
6.I can do a lot of things myself to cope with my condition	1	2	3	4	5
7.When it comes to managing my condition, I can only do what my doctor tells me to do	1	2	3	4	5
8.When I manage my personal life well, my condition does not flare as much	1	2	3	4	5
9.I have considerable ability to control my pain	1	2	3	4	5
10.I would feel helpless if I couldn't rely on other people for help with my condition	1	2	3	4	5
11.Usually, I can tell when my condition will flare up	1	2	3	4	5
12. No matter what I do, or how hard I try, I just can't seem to get relief from my pain	1	2	3	4	5
13.I am coping effectively with my condition	1	2	3	4	5
14.It seems as though fate and other factors beyond my control affect my condition	1	2	3	4	5
15.I want to learn as much as I can about my condition	1	2	3	4	5

7. What is the highest level of education you have completed?(please check only ONE answer)

No schooling ________
Elementary ________ grade________
Junior High ________ grade________
High School ________ grade________
Non-University ________ (Vocational, Technical, Nursing Schools)
University
  Diploma/ ________ (e.g.Hygienist)
  Certificate
  Bachelor's degree ________
  Medical degree ________
  Master's degree ________
  Doctorate ________

8. Currently, are you (check only one)

Employed full time? ____
Employed part time? ____
Unemployed? ____
Retired? ____
In school? ____
Keeping house? ____

9. How many hours a WEEK do you normally work in the items indicated in question 8? ________

10. What is your current marital status?

Single- never married ____
Now married/common law ____
Divorced/Separated ____
Widowed ____

11. Please check the number that comes closest to YOUR TOTAL INDIVIDUAL INCOME, for 1990, before tax and deductions.

Under $7,000 ____
$7,000-14,999 ____
$15,000-24,999 ____
$25,000-34,999 ____
$35,000-44,999 ____
$45,000-59,999 ____
$60,000 or more ____

12.Please check the number that comes closest to THE TOTAL INCOME OF ALL THE MEMBERS OF YOUR HOUSEHOLD for 1990, before tax and deductions

Under $7,000 ____
$7,000-14,999 ____
$15,000-24,999 ____
$25,000-34,999 ____
$35,000-44,999 ____
$45,000-59,999 ____
$60,000-79,999 ____
80,000 or more ____

13. Including professional, union, recreational, church groups etc., to how many groups and organizations do you belong? _______

14. Do you belong to the Arthritis Society chapter? _____

15. Check the answer that better reflects your attitude towards religion:

Religion is very important to me ____
Religion is somewhat important to me ____
Religion is not important to me ____

16. How often do you get together with your friends?

Daily or almost every day ____
1-3 times a week ____
1-3 times a month ____
Less than once a month ____
Never ____

17. How often do you get together with any neighbours just for a chat?

Daily or almost every day ____
1-3 times a week ____
1-3 times a month ____
Less than once a month ____
Never ____

18. Which of the following people live with you?

Husband/Wife ____
Children under 15 ____ How many children?____
Children 15 or over ____ How many children?____
Mother ____
Father ____
Brothers/Sisters ____
Other relatives/ friends ____
I live alone ____

19. Please check ONLY one of the following.

I leave my neighbourhood daily ____
I leave my neighbourhood 3-6 times/wk ____
I leave my neighbourhood less than 3 times/wk ____

20. Approximately, what amount of alcoholic beverages do you consume PER MONTH?

BEER ______ bottles/cans per MONTH
WINE (4-5 oz glass) ______ glasses per MONTH
SPIRITS (1.5 oz drink) ______ drinks per MONTH

21. At the present time, do you smoke cigarettes, cigars, pipe?_____ (circle which type or types)

I do not smoke _____

If you smoke, how many cigarettes, pipes or cigars do you smoke daily _____

APPENDIX 7

VARIABLE CODEBOOK

	VARIABLE NAME	VARIABLE DESCRIPTION AND VARIABLE CODES
v1	CASE	Case identification number
v2	NAME	Name initials
v3	ONCH	Certainty of onset in 1985, from clinical chart 0 probable onset in 1985 1 definite onset in 1985
v4	DR	Current rheumatologist (1 to 9)
v5	NORH	Number of rheumatologists seen
v6	DR2	Second rheumatologist seen codes as v4
v7	DR3	Third rheumatologist seen codes as v4
v8	HSC	Follow-up at the University of Alberta gold clinic 0 never 1 currently attending 2 previously attended
v9	SEX	0 female 1 male
v10	RES	current city of residence 0 Out of town 1 Edmonton 2 St Albert 3 Spruce Grove 4 Stony Plain 5 Sherwood Park 6 Fort Saskatchewan
v11	DOB	date of birth (mmddyy)
v12	AGE	age in years
v13	FSEEN	year of first assessment by a rheumatologist (last 2 digits)
v14	LSEEN	year of last assessment by a rheumatologist (last 2 digits)
v15	FUP	time period of follow-up by rheumatologists (months from first to last assessment by a rheumatologist)
v16	OUTCON	number of outpatient consults to a rheumatologist from 1985 to 1991, to a maximum of 12 consults per year. This variable is to be used to estimate minimum only.

v17	YRH	number of years from 1985 to 1991 inclusive that the patient was assessed at least once by a rheumatologist
v18	CHCR1	presence of criterion 1 of the ACR criteria for the diagnosis of rheumatoid arthritis as obtained from information included in patient's medical records criterion 1: morning stiffness > 1 hour 0 absent 1 present -1 not specified in medical records
v19	CHCR2	criterion 2: swelling of 3 or more joint areas codes as v17
v20	CHCR3	criterion 3: swelling of PIP, MCP or wrist joints codes as v17
v21	CHCR4	criterion 4: symmetrical swelling codes as v17
v22	CHCR5	criterion 5: rheumatoid nodules codes as v17
v23	CHCR6	criterion 6: rheumatoid factor codes as v17
v24	CHCR7	criterion 7: radiological changes codes as v17
v25	CHLABY	year closest to onset (1985) when laboratory tests (rheumatoid factors, CBC, ESR) where performed, as per medical records
v26	CHRF	rheumatoid factor as per chart (test closest to onset) 1 positive (≥ 40) 0 negative -1 not available
v27	CHHGB	hemoglobin (g/dL) as per chart (test closest to onset) -1 not available
v28	CHPL	platelets (10*9/L) as per chart (test closest to onset) -1 not available
v29	CHESR	sedimentation rate (mm/h) as per chart (test closest to onset) -1 not available
v30	DSEEN	date patient was assessed for the study (mmddyy)
v31	YSEEN	year patient was assessed for study 0 1991 1 1992

v32	PSEEN	physical space were assessment was conducted 1 outpatient clinic 2 patient's home 3 hospital ward (admitted patients) 4 nursery home
v33	CONTACT	mode of contacting patient 0 letter (spontaneous response from patient) 1 patient contacted directly (by phone or other route when no response was obtained after mailing 2 letters)
v34	ETHNIC	ethnic background 1 white 2 black 3 oriental 4 north-american indian 5 east-indian
v35	ON85	certainty of onset in 1985 0 probable 1 definite
v36	TYPEONS	type of onset 1 gradual 2 acute 3 palindromic
v37	DD	approximate duration of disease in months
v38	AGEONS	age at onset in years
v39	VISITFD	approximate number of annual visits to family physician as reported by patient (to a maximum of 12) -1 not reported
v40	DRUGINS	percentage of the price of prescribed drugs covered by medical insurance
v41	HYST	previous hysterectomy 0 no 1 yes -1 not reported -2 not applicable
v42	HYSTAGE	age at hysterectomy in years -1 not reported -2 not applicable
v43	ADMRA	number of admissions to hospital related to rheumatoid arthritis
v44	COMORB	number of concomitant diseases

v45	PSOR	diagnosis of psoriasis	
		0	no
		1	yes
		-1	unknown
v46	FH	family history of rheumatoid arthritis	
		0	no
		1	yes
		-1	unknown
v47	FHPS	family history of psoriasis	
		0	no
		1	yes
		-1	unknown
v48	DELBEF	number of deliveries before onset	
		-1	unknown
		-2	not applicable
v49	DELAFT	number of deliveries after onset	
		-1	unknown
		-2	not applicable
v50	MNP	age at menopause in years	
		0	premenopausal
		-1	unknown
		-2	not applicable
v51	BCP	total cumulative duration of use of contraceptive drugs in months	
		0	never used
		-1	unknown
		-2	not applicable
v52	STOPBCP	last year of use of contraceptive drugs (last 2 digits)	
		-1	unknown
		-2	not applicable
v53	COURSE	course of the disease	
		1	chronic (no remissions)
		2	remittive (≥ 1 remission lasting at least 2 months)
		3	palindromic (typical palindromic arthritis with attacks lasting hours or days; at least one flare should have lasted ≥ 6 weeks to comply with the ACR criteria)
		4	single flare lasting ≤ 36 months (single flares lasting longe were categorized as remittive)
v54	DURFL	duration of flare in months (only if v52=4)	
v55	EDPR	previous attendance to arthritis education program	
		0	no
		1	yes
		-1	unknown
v56	YEDPR	year of education program, last 2 digits (only if v55=1)	

v57	PHYS	previous use of physiotherapy services	
		0	no
		1	yes
		-1	unknown
v58	EXER	weekly frequency of therapeutic exercise (as taught by physiotherapist or education program)	
		0	never
		1	< once per week
		2	1-3 times per week
		3	> 3 times per week
		-1	not reported
v59	RECSP	weekly frequency of recreational exercise or sports	
		0	never
		1	< once per week
		2	1-3 times per week
		3	> 3 times per week
		-1	not reported
v60	SPBEFRA	engagement in physical activities or sports at least 3 times a week for at least 5 years before onset	
		0	no
		1	yes
		-1	not reported
v61	SURG	joint-related surgeries after onset	
		1	RA related
		2	osteoarthritis related
		3	fracture
		4	other
		-1	unknown
v62	TSURG1	type of surgery	
		1	carpal tunnel release
		2	tenotomy
		3	synovectomy
		4	knee replacement
		5	hip replacement
		6	extensor tendon repair
		7	hallux valgus correction
		8	arthrodesis
v63	TSURG2	type of surgery, second choice	
			codes as v62
v64	MED1	second line drug (drug 1) in current therapeutic regime	
		0	none
		1	chloroquine
		2	auranofin
		3	parenteral gold salts
		4	methotrexate
		5	d-penicilamine
		6	azathioprine
		7	sulphasalazine

		8 cyclophosphamide
v65	MED2	second line drug (drug 2) in current therapeutic regime codes as v64
v66	MED3	second line drug (drug 3) in current therapeutic regime codes as v64
v67	SLNOW	number of second line drugs in current therapeutic regime
v68	PREDNOW	current use of prednisone 0 no 1 yes -1 unknown
v69	DOSEP	current daily dosage of prednisone in mg
v70	REASPRN	reason why prednisone was prescribed 1 rheumatoid arthritis 2 side effect of drug for arthritis 3 concomitant disease -1 unknown
v71	SELFMED	previous or current use of oral or systemic alternative medicine (homeopathy, herbs) 0 no 1 yes -1 not reported
v72	DSELFMED	self medication used (alphanumeric variable)
v73	ACUP	previous or current use of acupunture for rheumatoid arthritis 0 no 1 yes -1 not reported
v74	VIT	regular vitamin intake 0 no 1 yes -1 not reported
v75	CORTINJ	approximate number of intraarticular cortisone injections since onset as reported by patient -1 not reported
v76	RADSYN	previous radiochemical synovectomy 0 no 1 yes -1 not reported
v77	MS	duration of morning stiffness, minutes -1 not reported
v78	PAIN	pain, visual analogue scale, mm -1 not completed

v79	HEIGHT	as reported by patient, cm -1 not reported
v80	WEIGHT	as reported by patient, Kg -1 not reported
v81	DH	dominant hand 1 right 2 left -1 not reported
v82	CR1	criterion 1 of the ACR criteria for the diagnosis of rheumatoid arthritis after the clinical, radiological and laboratory assessments in the study were completed criterion 1: morning stiffness > 1 hour 0 absent 1 currently present 2 currently absent but positive history 3 currently unknown but positive history -1 unknown
v83	CR2	criterion 2: swelling of 3 or more joint areas codes as v80
v84	CR3	criterion 3: swelling of PIP, MCP or wrist joints codes as v80
v85	CR4	criterion 4: symmetrical swelling codes as v80
v86	CR5	criterion 5: rheumatoid nodules codes as v80
v87	CR6	criterion 6: rheumatoid factor codes as v80
v88	CR7	criterion 7: radiological changes codes as v80
v89	TDJ	number of tender joints
v90	TDIND	tenderness index
v91	SWELB	elbow joint swelling 0 absent 1 unilateral 2 bilateral
v92	SWWR	wrist joint swelling 0 absent 1 unilateral 2 bilateral

v93	SWMCP	metacarpophalangeal joint area swelling	
		0	absent
		1	unilateral
		2	bilateral
v94	SWPIP	proximal interphalangeal joint area swelling	
		0	absent
		1	unilateral
		2	bilateral
v95	SWKNEE	knee swelling	
		0	absent
		1	unilateral
		2	bilateral
v96	SWANK	ankle swelling	
		0	absent
		1	unilateral
		2	bilateral
v97	SWJ	number of swollen joints	
v98	SWIND	articular index, swollen joints	
v99	ROMSP	range of motion of cervical spine	
		0	normal
		1	decreased
v100	ROMSH	range of motion of shoulder joints	
		0	normal
		1	unilateral decrease
		2	bilateral decrease
v101	ROMELB	range of motion of elbow joints	
		0	normal
		1	unilateral decrease
		2	bilateral decrease
v102	ROMWR	range of motion of wrist joints	
		0	normal
		1	unilateral decrease
		2	bilateral decrease
v103	ROMFIST	completeness of fist	
		0	normal
		1	unilateral decrease
		2	bilateral decrease
v104	ROMHIP	range of motion of hip joints	
		0	normal
		1	unilateral decrease
		2	bilateral decrease
v105	ROMKNEE	range of motion of knee joints	
		0	normal
		1	unilateral decrease

			2	bilateral decrease
v106	ROMANK	range of motion of ankle joints		
			0	normal
			1	unilateral decrease
			2	bilateral decrease
v107	ROMJ	number of joints with restricted range of motion		
v108	ROMIND	range of motion index		
v109	DEFH	hand deformities		
			0	no
			1	yes
v110	CD	cubital deviation		
			0	no
			1	yes
v111	MCPSL	metacarpophalangeal subluxation		
			0	no
			1	yes
v112	FDEF	finger deformities, swan-neck, boutonniere		
			0	no
			1	yes
v113	QUEST	questionnaire response		
			0	not completed
			1	completed as self-report questionnaire
			2	completed with assistance from interviewer
v114	HAQ	HAQ activities of daily life score		
			-1	not reported
v115	CHLIFE	changes in lifestyle secondary to rheumatoid arthritis		
			0	no
			1	yes
			-1	not reported

VARIABLES 116 TO 121 ONLY RECORDED IF V113=1

v116	CHL1	'I don't work anymore because of my arthritis'		
			0	no/not available
			1	yes
v117	CHL2	'I have changed occupations because of my arthritis'		
			0	no/not available
			1	yes
v118	CHL3	'I work less hours/wk because of my arthritis'		
			0	no/not available
			1	yes
v119	CHL4	'I socialize less with friends because of my arthritis'		
			0	no/not available

			1	yes
v120	CHL5	'My arthritis has damaged my family relationships'		
			0	no/not available
			1	yes
v121	CHL6	'My income has decreased because of my arthritis'		
			0	no/not available
			1	yes
V122	ATTIT	HAQ attitudes score		
			-1	not completed
v123	EDUC	education in years		
			1-12	highest school grade completed
			13	non-university (vocational, technical)
			14	university, diploma or certificate
			16	university, bachelor's degree
			18	university, master's, doctorate or medical degree
			-1	not reported
v124	EMPL	current employment status		
			1	full-time employed
			2	part-time employed
			3	unemployed (includes social assistance and disability pension)
			4	retired
			5	in school
			6	keeping house
			-1	not reported
v125	MARST	marital status		
			1	single-never married
			2	now married/common law
			3	divorced/separated
			4	widowed
			-1	not reported
v126	PINC	personal income before taxes for 1990		
			1	under $7,000
			2	$7,000-14,999
			3	$15,000-24,999
			4	$25,000-34,999
			5	$35,000-44,999
			6	$45,000-59,999
			7	$60,000 or more
			-1	not reported
v127	TINC	total household income before taxes for 1990		
			1	under $7,000
			2	$7,000-14,999
			3	$15,000-24,999
			4	$25,000-34,999
			5	$35,000-44,999
			6	$45,000-59,999
			7	$60,000-79,999

		8	$80,000
		-1	not reported
v128	MEMB	number of memberships in groups and organizations	
		-1	not reported
v129	ARSOC	membership in the Arthritis Society	
		0	no
		1	yes
		-1	nor reported
v130	REL	attitude towards religion	
		0	not important
		1	somewhat important
		2	very important
		-1	not reported
v131	FR	frequency of social gatherings with friends ('How often do you get together with your friends?')	
		0	never
		1	less than once a month
		2	1-3 times a month
		3	1-3 times a week
		4	daily or almost every day
		-1	not reported
v132	NEIGH	frequency of social encounters with neighbours ('How often do do you get together with neighbours just for a chat?')	
		0	never
		1	less than once a month
		2	1-3 times a month
		3	1-3 times a week
		4	daily or almost every day
		-1	not reported
v133	SHH	number of people sharing household	
		-1	not reported
v134	LEAVE	weekly frequency that patient leaves	
		1	less than 3/times/week
		2	3-6 times/week
		3	daily
		-1	not reported
v135	ALCOHOL	alcohol consumption (drinks/month)	
		-1	not reported
v136	TOBACCO	tobacco consumption (cigarettes, pipes and cigars/day)	
		-1	not reported
v137	MARST84	marital status in 1984	
		1	single-never married
		2	now married/common law
		3	divorced/separated
		4	widowed

		-1	not reported
v138	CHLOR		number of therapeutic courses with chloroquine

VARIABLES V139 TO V147 ONLY COMPLETED IF V138 ≥1

v139	CHLPR		physician first prescribing chloroquine
		1 to 9	Edmonton rheumatologist
		10	out of town rheumatologist
		11	other non-rheumatologist physicians (general practitioners, family physicians, internists, other specialists)
		12	drug trial
		-1	unknown
v140	CHLCH		rank selection of chloroquine as second-line drug (1st therapeutic course; e.g. 1st, 2nd, 3rd, etc choice)
v141	CHLST		year chloroquine was initially given (last 2 digits)
v142	CHLDT		total cumulative duration of therapy with chloroquine in months
v143	CHLCO		combination of cloroqine with other second line drugs
		0	never given in combination
		1	sometimes given in combination
		2	always given in combination
v144	CHLSE		side effects from chloroquine
		0	no
		1	yes, attributed to chloroquine
		2	yes, attributed to combination with another drug
v145	CHLSE1		description side effects from chloroquine (if v141=1)
		1	gastrointestinal
		2	mucocutaneous
		3	hematological
		4	renal
		5	ocular
		6	hepatic
		7	pneumonitis
		8	loss of taste
		9	malaise
		10	other
		-1	unknown
v146	CHLSE2		as v142, second choice

v147	CHLDC	discontinuation of chloroquine (last therapeutic course) 0 still on 1 toxicity 2 lack of effect 3 no longer needed 4 by patient 5 concomitant disease 6 pregnancy -1 unknown
v148	AURA	number of therapeutic courses with auranofin

VARIABLES V149 TO V157 ONLY COMPLETED IF V148 ≥1

v149	AUPR	physician first prescribing auranofin codes as v139
v150	AUCH	rank selection of auranofin as second-line drug (1st therapeutic course; e.g. 1st, 2nd, 3rd, etc choice)
v151	AUST	year auranofin was initially given (last 2 digits)
v152	AUDT	total cumulative duration of therapy with auranofin in months
v153	AUCO	combination of auranofin with other second line drugs codes as v143
v154	AUSE	side effects from auranofin 0 no 1 yes, attributed to auranofin 2 yes, attributed to combination with another drug
v155	AUSE1	description side effects from auranofin (if v154 ≥1) codes as v145
v156	AUSE2	as v155, second choice
v157	AUDC	discontinuation of auranofin (last therapeutic course) codes as v147
v158	GOLD	number of therapeutic courses with parenteral gold salts

VARIABLES V159 TO V167 ONLY COMPLETED IF V158 ≥1

v159	GOPR	physician first prescribing parenteral gold salts codes as v139
v160	GOCH	rank selection of parenteral gold salts as second-line drug (1st therapeutic course; e.g. 1st, 2nd, 3rd, etc choice)
v161	GOST	year parenteral gold salts were initially given (last 2 digits)
v162	GODT	total cumulative duration of therapy with parenteral gold salts in months
v163	GOCO	combination of parenteral gold salts with other second line drugs codes as v143

v164	GOSE	side effects from parenteral gold salts 0 no 1 yes, attributed to auranofin 2 yes, attributed to combination with another drug
v165	GOSE1	description side effects from parenteral gold salts (if v164 ≥1) codes as v145
v166	GOSE2	as v165, second choice
v167	GODC	discontinuation of parenteral gold salts (last therapeutic course) codes as v147
v168	MTX	number of therapeutic courses with methotrexate

VARIABLES V169 TO V177 ONLY COMPLETED IF V168 ≥1

v169	MTPR	physician first prescribing methotrexate codes as v139
v170	MTCH	rank selection of methotrexate as second-line drug (1st therapeutic course; e.g. 1st, 2nd, 3rd, etc choice)
v171	MTST	year methotrexate was initially given (last 2 digits)
v172	MTDT	total cumulative duration of therapy with methotrexate in months
v173	MTCO	combination of methotrexate with other second line drugs codes as v143
v174	MTSE	side effects from methotrexate 0 no 1 yes, attributed to methotrexate 2 yes, attributed to combination with another drug
v175	MTSE1	description side effects from methotrexate (if v174 ≥ 1) codes as v145
v176	MTSE2	as v175, second choice
v177	MTDC	discontinuation of methotrexate (last therapeutic course) codes as v147
v178	DPEN	number of therapeutic courses with d-penicilamine

VARIABLES V179 TO V187 ONLY COMPLETED IF V178 ≥1

v179	DPPR	physician first prescribing d-penicilamine codes as v139
v180	DPCH	rank selection of d-penicilamine as second-line drug (1st therapeutic course; e.g. 1st, 2nd, 3rd, etc choice)
v181	DPST	year d-penicilamine was initially given (last 2 digits)

v182	DPDT	total cumulative duration of therapy with d-penicilamine in months
v183	DPCO	combination of d-penicilamine with other second line drugs codes as v143
v184	DPSE	side effects from d-penicilamine 0 no 1 yes, attributed to d-penicilamine 2 yes, attributed to combination with another drug
v185	DPSE1	description side effects from d-penicilamine (if v184 ≥1) codes as v145
v186	DPSE2	as v185, second choice
v187	DPDC	discontinuation of d-penicilamine (last therapeutic course) codes as v147
v188	AZT	number of therapeutic courses with azathioprine

VARIABLES V189 TO V157 ONLY COMPLETED IF V198 ≥1

v189	AZPR	physician first prescribing azathioprine codes as v139
v190	AZCH	rank selection of azathioprine as second-line drug (1st therapeutic course; e.g. 1st, 2nd, 3rd, etc choice)
v191	AZST	year azathioprine was initially given (last 2 digits)
v192	AZDT	total cumulative duration of therapy with azathioprine in months
v193	AZCO	combination of azathioprine with other second line drugs codes as v143
v194	AZSE	side effects from azathioprine 0 no 1 yes, attributed to azathioprine 2 yes, attributed to combination with another drug
v195	AZSE1	description side effects from azathioprine (if v194 ≥1) codes as v145
v196	AZSE2	as v195, second choice
v197	AZDC	discontinuation of azathioprine (last therapeutic course) codes as v147
v198	SZRA	number of therapeutic courses with sulfasalazine

VARIABLES V199 TO V207 ONLY COMPLETED IF V198 ≥1

v199	SZPR	physician first prescribing sulfasalazine codes as v139

v200	SZCH	rank selection of sulfasalazine as second-line drug (1st therapeutic course; e.g. 1st, 2nd, 3rd, etc choice)
v201	SZST	year sulfasalazine was initially given (last 2 digits)
v202	SZDT	total cumulative duration of therapy with sulfasalazine in months
v203	SZCO	combination of sulfasalazine with other second line drugs codes as v143
v204	SZSE	side effects from sulfasalazine 0 no 1 yes, attributed to sulfasalazine 2 yes, attributed to combination with another drug
v205	SZSE1	description side effects from sulfasalazine (if v204 ≥ 1) codes as v145
v206	SZSE2	as v205, second choice
v207	SZDC	discontinuation of sulfasalazine (last therapeutic course) codes as v147
v208	CYRA	number of therapeutic courses with cyclophosphamide

VARIABLES V209 TO V217 ONLY COMPLETED IF V208 ≥ 1

v209	CYPR	physician first prescribing cyclophosphamide codes as v139
v210	CYCH	rank selection of cyclophosphamide as second-line drug (1st therapeutic course; e.g. 1st, 2nd, 3rd, etc choice)
v211	CYST	year cyclophosphamide was initially given (last 2 digits)
v212	CYDT	total cumulative duration of therapy with cyclophosphamide in months
v213	CYCO	combination of cyclophosphamide with other second line drugs codes as v143
v214	CYSE	side effects from cyclophosphamide 0 no 1 yes, attributed to cyclophosphamide 2 yes, attributed to combination with another drug
v215	CYSE1	description side effects from cyclophosphamide (if v214 ≥ 1) codes as v145
v218	CYSE2	as v215, second choice
v217	CYDC	discontinuation of cyclophosphamide (last therapeutic course) codes as v147
V218	PRED	number of therapeutic courses of prednisone

VARIABLES V219 TO V222 ONLY COMPLETED IF V218 ≥1

v219	PREDPR	physician prescribing prednisone codes as v139
v220	STPRED	year prednisone was started (last 2 digits)
v221	DTPRED	total cumulative duration of therapy with prednisone in months
v222	RPRED	1 rheumatoid arthritis 2 side effect of drug for arthritis 3 concomitant disease
v223	STSL	year second line therapy was initiated (last 2 digits) 0 never
v224	FSL	first second-line drug prescribed codes as v64
v225	FSLPR	physician precribing first second-line drug codes as v139
v226	DURSL	total cumulative duration of therapy with ANY second line drug (minimum of 3 continuous months of therapy with each single drug required to be included in total)
v227	COSL	number of different combinations of 2 or more second line drugs used

VARIABLES V228 TO V233 TO BE COMPLETED ONLY IF V227 ≥1

v228	C1PR	physician prescribing 1st combination codes as v139
v229	C1D1	drug 1 used in the 1st combination of second line drugs codes as v64
v230	C1D2	drug 2 used in the 1st combination of second line drugs codes as v64
v231	C1D3	drug 3 used in the 1st combination of second line drugs codes as v64
v232	C1DT	duration of therapy with 1st combination, months
v233	C1SO	continuation of therapy with combined drugs 0 all drugs in combination discontinued 1 still on combined therapy 2 combined therapy modified, but patient still receiving at least 1 of the drugs in the combination

VARIABLES V234 TO V239 ONLY COMPLETED IF V227 =2

v234	C2PR	physician prescribing 1st combination codes as v139
v235	C2D1	drug 1 used in the 1st combination of second line drugs codes as v64
v236	C2D2	drug 2 used in the 1st combination of second line drugs codes as v64
v237	C2D3	drug 3 used in the 1st combination of second line drugs codes as v64
v238	C2DT	duration of therapy with 1st combination, months
v239	C2SO	continuation of therapy with combined drugs 0 all drugs in combination discontinued 1 still on combined therapy 2 combined therapy modified, but patient still receiving at least 1 of the drugs in the combination
v240	XRERS	radiologic score - erosions -1 not available
v241	XRJSN	radiological score - joint space narrowing -1 not available
v242	JAOP	juxta-articular osteoporosis 0 no 1 yes -1 not available
v243	WRSC	radiological score - wrist joints -1 not available
v244	FRULN	fracture ulnar styloid 0 no 1 definite 2 equivocal -1 not available
v245	HGB	hemoglobin, g/dL -1 not available
v246	PLAT	platelets 10*9/L -1 not available
v247	ESR	sedimentation rate mm/hour -1 not available
v248	RF	rheumatoid factor titre -1 not available

v249	FANA	antinuclear antibodies titre	
		-1	not available
v250	PFANA	FANA patterns (if v249 ≥1)	
		1	homogeneous
		2	nucleolar
		3	speckled
		4	rim
		-1	not avilable
v251	RDUF	RDU antinuclear antibodies	
		0	negative
		1	positive
		2	weak
		-1	not available
v252	PRDU	pattern of RDU antinuclear antibodies (if v251 ≥1)	
		1	homogenous
		2	nucleolar
		3	fine speckled
		4	coarse speckled
		5	rim
		-1	not available
v253	ENA	extractable nuclear antigens	
		0	negative
		1	positive
		-1	not available
v254	TENA	type of extractable nuclear antigens (if v252=1)	
		1	RNP
		2	Sm
		3	SSA
		4	SSB
		5	unidentified line
		-1	not available
v255	DNA	anti-DNA, % binding (if v250=1 or v252=1)	
		-1	not available
v256	HLA DR4	HLA DR4 status	
		0	negative
		1	positive

APPENDIX 8

LISREL COMPUTER OUTPUT - MODEL 1

(edited)

```
14 Dec 92   SPSS-X RELEASE 3.0 FOR IBM MTS
13:18:48    University of Alberta

   1  0  title 'Prognosis in RA 1'
   2  0  file handle #8/name='covmatra'
   3  0  input program
   4  0  numeric a
   5  0  end file
   6  0  end input program
   7  0  user proc name=lisrel
   8  0  OUTCOME IN RA-SINGLE INDICATORS-1                   outcome 1
   9  0  DA NI=14 NO=128 MA=CM
  10  0  CM UN=8 FU FO
  11  0  (14F10.4)
  12  0  LA
  13  0  'age' 'sex' 'rmarst' 'dursl' 'rstsl' 'rgodt' 'rf' 'educ' 'tinc'
  14  0  'xraysc' 'tdj' 'swj' 'romj' 'mhaq'
  15  0  SE
  16  0  'educ' 'tinc' 'swj' 'mhaq'
  17  0  'age' 'sex' 'rmarst' 'rf'/
  18  0  MO NY=4 NX=4 NE=4 NK=4 LY=ID LX=ID  BE=FU,FI GA=FU,FI C
  19  0  PH=FU,FR PS=DI,FR TE=DI,FI TD=DI,FI
  20  0  FR BE(2,1) BE(4,1) BE(4,2) BE(4,3)
  21  0  FR GA(1,1) GA(1,2) GA(2,1) GA(2,2) GA(2,3) GA(3,4) GA(3,2) GA(4,1)
  22  0  VA 0.8149 TE(1,1)
  23  0  VA 0.4217 TE(2,2)
  24  0  VA 3.1216 TE(3,3)
  25  0  VA 0.0217 TE(4,4)
  26  0  VA 0.0244 TD(4,4)
  27  0  OU ML AL TM=10
  28  0  end user
There are 64984 bytes of memory available.
 The largest contiguous area has 64984 bytes.

                         L I S R E L  VI - VERSION 6.6
                                       BY
                        KARL G JORESKOG AND DAG SORBOM
-OUTCOME IN RA-SINGLE INDICATORS-1                   outcome 1
-THE FOLLOWING LISREL CONTROL LINES HAVE BEEN READ :

 DA NI=14 NO=128 MA=CM
 CM UN=8 FU FO
 (14F10.4)
 LA
 'age' 'sex' 'rmarst' 'dursl' 'rstsl' 'rgodt' 'rf' 'educ' 'tinc'
 'xraysc' 'tdj' 'swj' 'romj' 'mhaq'
 SE
 'educ' 'tinc' 'swj' 'mhaq'
 'age' 'sex' 'rmarst' 'rf'/
 MO NY=4 NX=4 NE=4 NK=4 LY=ID LX=ID  BE=FU,FI GA=FU,FI C
 PH=FU,FR PS=DI,FR TE=DI,FI TD=DI,FI
 FR BE(2,1) BE(4,1) BE(4,2) BE(4,3)
 FR GA(1,1) GA(1,2) GA(2,1) GA(2,2) GA(2,3) GA(3,4) GA(3,2) GA(4,1)
 VA 0.8149 TE(1,1)
 VA 0.4217 TE(2,2)
 VA 3.1216 TE(3,3)
 VA 0.0217 TE(4,4)
 VA 0.0244 TD(4,4)
 OU ML AL TM=10
```

```
                        L I S R E L  VI - VERSION 6.6
-OUTCOME IN RA-SINGLE INDICATORS-1                 outcome 1
                        NUMBER OF INPUT VARIABLES 14
                        NUMBER OF Y - VARIABLES    4
                        NUMBER OF X - VARIABLES    4
                        NUMBER OF ETA - VARIABLES  4
                        NUMBER OF KSI - VARIABLES  4
                        NUMBER OF OBSERVATIONS   128


          COVARIANCE MATRIX TO BE ANALYZED
              educ      tinc      swj       mhaq      age       sex       rmarst    rf
           --------  --------  --------  --------  --------  --------  --------  --------
 educ         8.149
 tinc         2.615     4.217
 swj         -0.893    -0.205    31.216
 mhaq        -0.339    -0.341     0.825     0.217
 age        -16.982   -12.394    -4.530     1.735   178.858
 sex         -0.133    -0.034    -0.266     0.004     0.472     0.210
 rmarst      -0.105    -0.496     0.208     0.024     0.633    -0.046     0.216
 rf           0.062     0.238     0.825    -0.001    -0.760     0.017    -0.037     0.244
-          DETERMINANT = 0.102646E+03


 PARAMETER SPECIFICATIONS

          BETA
              educ      tinc      swj       mhaq
           --------  --------  --------  --------
 educ             0         0         0         0
 tinc             1         0         0         0
 swj              0         0         0         0
 mhaq             2         3         4         0

          GAMMA
              age       sex       rmarst    rf
           --------  --------  --------  --------
 educ             5         6         0         0
 tinc             7         8         9         0
 swj              0        10         0        11
 mhaq            12         0         0         0

          PHI
              age       sex       rmarst    rf
           --------  --------  --------  --------
 age             13
 sex             14        15
 rmarst          16        17        18
 rf              19        20        21        22

          PSI
              educ      tinc      swj       mhaq
           --------  --------  --------  --------
                 23        24        25        26
          THETA EPS
              educ      tinc      swj       mhaq
           --------  --------  --------  --------
                  0         0         0         0
          THETA DELTA
              age       sex       rmarst    rf
           --------  --------  --------  --------
                  0         0         0         0
```

```
-LISREL ESTIMATES (MAXIMUM LIKELIHOOD)

             BETA
                educ        tinc        swj         mhaq
              --------    --------    --------    --------
  educ          0.000       0.000       0.000       0.000
  tinc          0.228       0.000       0.000       0.000
  swj           0.000       0.000       0.000       0.000
  mhaq         -0.009      -0.064       0.029       0.000

           GAMMA
                age         sex         rmarst      rf
              --------    --------    --------    --------
  educ         -0.094      -0.425       0.000       0.000
  tinc         -0.039      -0.408      -2.153       0.000
  swj           0.000      -1.566       0.000       3.848
  mhaq          0.005       0.000       0.000       0.000

             PHI
                age         sex         rmarst      rf
              --------    --------    --------    --------
  age         178.858
  sex           0.472       0.210
  rmarst        0.633      -0.046       0.217
  rf           -0.763       0.017      -0.036       0.219

           PSI
                educ        tinc        swj         mhaq
              --------    --------    --------    --------
                5.684       1.645      24.543       0.138

           THETA EPS
                educ        tinc        swj         mhaq
              --------    --------    --------    --------
                0.815       0.422       3.122       0.022

             THETA DELTA
                age         sex         rmarst      rf
              --------    --------    --------    --------
                0.000       0.000       0.000       0.024

             SQUARED MULTIPLE CORRELATIONS FOR Y - VARIABLES
                educ        tinc        swj         mhaq
              --------    --------    --------    --------
                0.900       0.900       0.900       0.900

             TOTAL COEFFICIENT OF DETERMINATION FOR Y - VARIABLES IS

  SQUARED MULTIPLE CORRELATIONS FOR X - VARIABLES
                age         sex         rmarst      rf
              --------    --------    --------    --------
                1.000       1.000       1.000       0.900

   SQUARED MULTIPLE CORRELATIONS FOR STRUCTURAL EQUATIONS
                educ        tinc        swj         mhaq
              --------    --------    --------    --------
                0.225       0.560       0.127       0.281

        TOTAL COEFFICIENT OF DETERMINATION FOR STRUCTURAL EQUATIONS  IS  0.625

-                  MEASURES OF GOODNESS OF FIT FOR THE WHOLE MODEL :
-     CHI-SQUARE WITH  10 DEGREES OF FREEDOM IS      9.81 (PROB. LEVEL = 0.457)
-                          GOODNESS OF FIT INDEX IS 0.981
-                     ADJUSTED GOODNESS OF FIT INDEX IS 0.974
-                      ROOT MEAN SQUARE RESIDUAL IS      0.297
```

```
-MODIFICATION INDICES

         BETA
            educ       tinc       swj        mhaq
         --------   --------   --------   --------
educ        0.000      0.395      1.236      1.453
tinc        0.000      0.000      0.042      0.967
swj         0.986      1.561      0.000      1.129
mhaq        0.000      0.000      0.000      0.000

         GAMMA
            age        sex        rmarst     rf
         --------   --------   --------   --------
educ        0.000      0.000      0.395      0.002
tinc        0.000      0.000      0.000      3.851
swj         0.020      0.000      1.597      0.000
mhaq        0.000      0.117      1.849      0.176

         PHI
            age        sex        rmarst     rf
         --------   --------   --------   --------
age         0.000
sex         0.000      0.000
rmarst      0.000      0.000      0.000
rf          0.000      0.000      0.000      0.000

         PSI
            educ       tinc       swj        mhaq
         --------   --------   --------   --------
            0.000      0.000      0.000      0.000

         THETA EPS
            educ       tinc       swj        mhaq
         --------   --------   --------   --------
            1.834      1.760      0.306      0.000

         THETA DELTA
            age        sex        rmarst     rf
         --------   --------   --------   --------
            2.649      0.019      3.851      0.717

        MAXIMUM MODIFICATION INDEX IS    3.85 FOR ELEMENT ( 2, 4) OF GAMMA


STANDARD ERRORS

         BETA
            educ       tinc       swj        mhaq
         --------   --------   --------   --------
educ        0.000      0.000      0.000      0.000
tinc        0.058      0.000      0.000      0.000
swj         0.000      0.000      0.000      0.000
mhaq        0.017      0.024      0.007      0.000

         GAMMA
            age        sex        rmarst     rf
         --------   --------   --------   --------
educ        0.017      0.495      0.000      0.000
tinc        0.011      0.290      0.285      0.000
swj         0.000      1.027      0.000      1.061
mhaq        0.003      0.000      0.000      0.000

         PHI
            age        sex        rmarst     rf
         --------   --------   --------   --------
age        22.445
sex         0.546      0.026
rmarst      0.555      0.019      0.027
rf          0.589      0.020      0.021      0.031
```

```
          PSI
             educ        tinc        swj         mhaq
          ________    ________    ________    ________
             0.816       0.265       3.516       0.021

          THETA EPS
             educ        tinc        swj         mhaq
          ________    ________    ________    ________
             0.000       0.000       0.000       0.000

          THETA DELTA
             age         sex         rmarst      rf
          ________    ________    ________    ________
             0.000       0.000       0.000       0.000


 -T-VALUES

          BETA
             educ        tinc        swj         mhaq
          ________    ________    ________    ________
 educ        0.000       0.000       0.000       0.000
 tinc        3.948       0.000       0.000       0.000
 swj         0.000       0.000       0.000       0.000
 mhaq       -0.535      -2.653       4.088       0.000

          GAMMA
             age         sex         rmarst      rf
          ________    ________    ________    ________
 educ       -5.531      -0.860       0.000       0.000
 tinc       -3.490      -1.407      -7.543       0.000
 swj         0.000      -1.525       0.000       3.627
 mhaq        1.561       0.000       0.000       0.000

          PHI
             age         sex         rmarst      rf
          ________    ________    ________    ________
 age         7.969
 sex         0.864       7.969
 rmarst      1.140      -2.389       7.969
 rf         -1.294       0.854      -1.732       7.171

          PSI
             educ        tinc        swj         mhaq
          ________    ________    ________    ________
             6.969       6.220       6.981       6.707

          THETA EPS
             educ        tinc        swj         mhaq
          ________    ________    ________    ________
             0.000       0.000       0.000       0.000

          THETA DELTA
             age         sex         rmarst      rf
          ________    ________    ________    ________
             0.000       0.000       0.000       0.000


 -TOTAL EFFECTS

          TOTAL EFFECTS OF KSI ON  ETA
             age         sex         rmarst      rf
          ________    ________    ________    ________
 educ       -0.094      -0.425       0.000       0.000
 tinc       -0.060      -0.505      -2.153       0.000
 swj         0.000      -1.566       0.000       3.848
 mhaq        0.010      -0.010       0.138       0.113
```

```
         TOTAL EFFECTS OF KSI ON  Y
            age          sex          rmarst      rf
          --------     --------     --------    --------
educ        -0.094       -0.425        0.000       0.000
tinc        -0.060       -0.505       -2.153       0.000
swj          0.000       -1.566        0.000       3.848
mhaq         0.010       -0.010        0.138       0.113

         TOTAL EFFECTS OF ETA ON  ETA
            educ         tinc         swj         mhaq
          --------     --------     --------    --------
educ         0.000        0.000        0.000       0.000
tinc         0.228        0.000        0.000       0.000
swj          0.000        0.000        0.000       0.000
mhaq        -0.024       -0.064        0.029       0.000

-LARGEST EIGENVALUE OF (I-BETA)*(I-BETA)-TRANSPOSED (STABILITY INDEX) IS   0.052


-FIRST ORDER DERIVATIVES

         BETA
            educ         tinc         swj         mhaq
          --------     --------     --------    --------
educ         0.000       -0.021        0.193       0.007
tinc        -0.000       -0.000       -0.063       0.016
swj          0.043        0.038        0.000      -0.004
mhaq         0.000       -0.000        0.000      -0.000

         GAMMA
            age          sex          rmarst      rf
          --------     --------     --------    --------
educ        -0.000       -0.000        0.010      -0.001
tinc         0.000       -0.000        0.000      -0.052
swj          0.031       -0.000       -0.010       0.000
mhaq        -0.000       -0.034        0.106       0.038

         PHI
            age          sex          rmarst      rf
          --------     --------     --------    --------
age         -0.000
sex         -0.000        0.000
rmarst      -0.000        0.000        0.000
rf          -0.000       -0.000       -0.000       0.000

         PSI
            educ         tinc         swj         mhaq
          --------     --------     --------    --------
educ         0.000
tinc        -0.000       -0.000
swj          0.008        0.006        0.000
mhaq        -0.003        0.130       -0.008      -0.000

         THETA EPS
            educ         tinc         swj         mhaq
          --------     --------     --------    --------
educ        -0.001
tinc        -0.001        0.017
swj          0.008        0.001        0.000
mhaq        -0.032        0.130       -0.008      -0.000

         THETA DELTA
            age          sex          rmarst      rf
          --------     --------     --------    --------
age         -0.000
sex          0.003        0.005
rmarst      -0.003       -0.018       -0.150
rf          -0.016       -0.089       -0.395       0.044
```

```
-STANDARDIZED SOLUTION

         LAMBDA Y
            educ       tinc       swj        mhaq
          --------   --------   --------   --------
 educ       2.708      0.000      0.000      0.000
 tinc       0.000      1.935      0.000      0.000
 swj        0.000      0.000      5.301      0.000
 mhaq       0.000      0.000      0.000      0.439

         LAMBDA X
            age        sex        rmarst     rf
          --------   --------   --------   --------
 age       13.374      0.000      0.000      0.000
 sex        0.000      0.459      0.000      0.000
 rmarst     0.000      0.000      0.465      0.000
 rf         0.000      0.000      0.000      0.468

         BETA
            educ       tinc       swj        mhaq
          --------   --------   --------   --------
 educ       0.000      0.000      0.000      0.000
 tinc       0.320      0.000      0.000      0.000
 swj        0.000      0.000      0.000      0.000
 mhaq      -0.057     -0.282      0.354      0.000

         GAMMA
            age        sex        rmarst     rf
          --------   --------   --------   --------
 educ      -0.463     -0.072      0.000      0.000
 tinc      -0.269     -0.097     -0.518      0.000
 swj        0.000     -0.136      0.000      0.340
 mhaq       0.156      0.000      0.000      0.000

         PHI
            age        sex        rmarst     rf
          --------   --------   --------   --------
 age        1.000
 sex        0.077      1.000
 rmarst     0.102     -0.217      1.000
 rf        -0.122      0.080     -0.164      1.000

         PSI
            educ       tinc       swj        mhaq
          --------   --------   --------   --------
            0.775      0.440      0.873      0.719



         CORRELATION MATRIX FOR ETA
            educ       tinc       swj        mhaq
          --------   --------   --------   --------
 educ       1.000
 tinc       0.473      1.000
 swj        0.032      0.048      1.000
 mhaq      -0.252     -0.367      0.330      1.000


         CORRELATION MATRIX FOR Y
            educ       tinc       swj        mhaq
          --------   --------   --------   --------
 educ       1.000
 tinc       0.473      1.000
 swj        0.032      0.048      1.000
 mhaq      -0.252     -0.367      0.330      1.000
```

```
               REGRESSION MATRIX ETA ON KSI (STANDARDIZED)
                  age          sex          rmarst       rf
              --------     --------     --------     --------
educ            -0.463       -0.072        0.000        0.000
tinc            -0.417       -0.120       -0.518        0.000
swj              0.000       -0.136        0.000        0.340
mhaq             0.300       -0.010        0.146        0.120

               REGRESSION MATRIX Y ON X (STANDARDIZED)
                  age          sex          rmarst       rf
              --------     --------     --------     --------
educ            -0.463       -0.072        0.000        0.000
tinc            -0.417       -0.120       -0.518        0.000
swj              0.000       -0.136        0.000        0.340
mhaq             0.300       -0.010        0.146        0.120


          29 COMMAND LINES READ.
           0 ERRORS DETECTED.
           0 WARNINGS ISSUED.
           2 SECONDS CPU TIME.
           8 SECONDS ELAPSED TIME.
             END OF JOB.
```

APPENDIX 9

LISREL COMPUTER OUTPUT - MODEL 3

(edited)

```
9 Dec 92   SPSS-X RELEASE 3.0 FOR IBM MTS
9:54:47    University of Alberta

    1  0  title 'Prognosis in RA 1'
    2  0  file handle #8/name='covmatra'
    3  0  input program
    4  0  numeric a
    5  0  end file
    6  0  end input program
    7  0  user proc name=lisrel
    8  0  OUTCOME IN RA-SINGLE INDICATORS                outcome 3
    9  0  DA NI=14 NO=128 MA=CM
   10  0  CM UN=8 FU FO
   11  0  (14F10.4)
   12  0  LA
   13  0  'age' 'sex' 'rmarst' 'dursl' 'rstsl' 'rgodt' 'rf' 'educ' 'tinc'
   14  0  'xraysc' 'tdj' 'swj' 'romj' 'mhaq'
   15  0  SE
   16  0  'educ' 'tinc' 'swj' 'xraysc' 'mhaq'
   17  0  'age' 'sex' 'rmarst' 'rf'/
   18  0  MO NY=5 NX=4 NE=5 NK=4 LY=ID LX=ID  BE=FU,FI GA=FU,FI C
   19  0  PH=FU,FR PS=DI,FR TE=DI,FI TD=DI,FI
   20  0  FR BE(2,1) BE(5,1) BE(5,2) BE(5,3) BE(4,3)
   21  0  FR GA(1,1) GA(1,2) GA(2,1) GA(2,2) GA(2,3) GA(3,2) GA(3,4)
   22  0  FR GA(4,1) GA (4,4) GA (5,1)
   23  0  PL GA(2,3)
   24  0  VA 0.8149 TE(1,1)
   25  0  VA 0.4217 TE(2,2)
   26  0  VA 3.1216 TE(3,3)
   27  0  VA 6.6621 TE(4,4)
   28  0  VA 0.0217 TE(5,5)
   29  0  VA 0.0244 TD(4,4)
   30  0  OU ML AL TM=15
   31  0  end user



                          L I S R E L  VI - VERSION 6.6
                                       BY
                          KARL G JORESKOG AND DAG SORBOM
-OUTCOME IN RA-SINGLE INDICATORS                 outcome 3
-THE FOLLOWING LISREL CONTROL LINES HAVE BEEN READ :


 DA NI=14 NO=128 MA=CM
 CM UN=8 FU FO
 (14F10.4)
 LA
 'age' 'sex' 'rmarst' 'dursl' 'rstsl' 'rgodt' 'rf' 'educ' 'tinc'
 'xraysc' 'tdj' 'swj' 'romj' 'mhaq'
 SE
 'educ' 'tinc' 'swj' 'xraysc' 'mhaq'
 'age' 'sex' 'rmarst' 'rf'/
 MO NY=5 NX=4 NE=5 NK=4 LY=ID LX=ID  BE=FU,FI GA=FU,FI C
 PH=FU,FR PS=DI,FR TE=DI,FI TD=DI,FI
 FR BE(2,1) BE(5,1) BE(5,2) BE(5,3) BE(4,3)
 FR GA(1,1) GA(1,2) GA(2,1) GA(2,2) GA(2,3) GA(3,2) GA(3,4)
 FR GA(4,1) GA (4,4) GA (5,1)
 PL GA(2,3)
 VA 0.8149 TE(1,1)
 VA 0.4217 TE(2,2)
 VA 3.1216 TE(3,3)
 VA 6.6621 TE(4,4)
 VA 0.0217 TE(5,5)
 VA 0.0244 TD(4,4)
 OU ML AL TM=15
```

```
                              L I S R E L  VI - VERSION 6.6
-OUTCOME IN RA-SINGLE INDICATORS                     outcome 3
                              NUMBER OF INPUT VARIABLES 14
                              NUMBER OF Y - VARIABLES    5
                              NUMBER OF X - VARIABLES    4
                              NUMBER OF ETA - VARIABLES  5
                              NUMBER OF KSI - VARIABLES  4
                              NUMBER OF OBSERVATIONS   128

0        COVARIANCE MATRIX TO BE ANALYZED
0           educ      tinc      swj       xraysc    mhaq      age       sex       rmarst    rf
+         --------  --------  --------  --------  --------  --------  --------  --------
 -------
 educ          8.149
 tinc          2.615     4.217
 swj          -0.893    -0.205    31.216
 xraysc       -1.434    -1.928    16.268    66.621
 mhaq         -0.339    -0.341     0.825     0.573     0.217
 age         -16.982   -12.394    -4.530    11.930     1.735   178.858
 sex          -0.133    -0.034    -0.266     0.353     0.004     0.472     0.210
 rmarst       -0.105    -0.496     0.208     0.103     0.024     0.633    -0.046     0.216
 rf            0.062     0.238     0.825     0.380    -0.001    -0.760     0.017    -0.037
0.244
-        DETERMINANT = 0.570161E+04


-PARAMETER SPECIFICATIONS
         BETA
            educ      tinc      swj       xraysc    mhaq
          --------  --------  --------  --------  --------
 educ            0         0         0         0         0
 tinc            1         0         0         0         0
 swj             0         0         0         0         0
 xraysc          0         0         2         0         0
 mhaq            3         4         5         0         0
         GAMMA
            age       sex       rmarst    rf
          --------  --------  --------  --------
 educ            6         7         0         0
 tinc            8         9        10         0
 swj             0        11         0        12
 xraysc         13         0         0        14
 mhaq           15         0         0         0
         PHI
            age       sex       rmarst    rf
          --------  --------  --------  --------
 age            16
 sex            17        18
 rmarst         19        20        21
 rf             22        23        24        25
         PSI
            educ      tinc      swj       xraysc    mhaq
          --------  --------  --------  --------  --------
                26        27        28        29        30
         THETA EPS
            educ      tinc      swj       xraysc    mhaq
          --------  --------  --------  --------  --------
                 0         0         0         0         0
         THETA DELTA
            age       sex       rmarst    rf
          --------  --------  --------  --------
                 0         0         0         0
```

```
LISREL ESTIMATES (MAXIMUM LIKELIHOOD)

         BETA
            educ        tinc        swj        xraysc      mhaq
          ________    ________    ________    ________    ________
educ        0.000       0.000       0.000       0.000       0.000
tinc        0.229       0.000       0.000       0.000       0.000
swj         0.000       0.000       0.000       0.000       0.000
xraysc      0.000       0.000       0.592       0.000       0.000
mhaq       -0.009      -0.064       0.029       0.000       0.000

         GAMMA
            age         sex         rmarst      rf
          ________    ________    ________    ________
educ       -0.094      -0.425       0.000       0.000
tinc       -0.039      -0.408      -2.153       0.000
swj         0.000      -1.494       0.000       3.841
xraysc      0.081       0.000       0.000      -0.170
mhaq        0.005       0.000       0.000       0.000

         PHI
            age         sex         rmarst      rf
          ________    ________    ________    ________
age       178.858
sex         0.472       0.210
rmarst      0.633      -0.046       0.216
rf         -0.763       0.017      -0.036       0.219

         PSI
            educ        tinc        swj         xraysc      mhaq
          ________    ________    ________    ________    ________
            5.684       1.645      24.600      49.511       0.138

         THETA EPS
            educ        tinc        swj         xraysc      mhaq
          ________    ________    ________    ________    ________
            0.815       0.422       3.122       6.662       0.022

         THETA DELTA
            age         sex         rmarst      rf
          ________    ________    ________    ________
            0.000       0.000       0.000       0.024

         SQUARED MULTIPLE CORRELATIONS FOR Y - VARIABLES
            educ        tinc        swj         xraysc      mhaq
          ________    ________    ________    ________    ________
            0.900       0.900       0.900       0.900       0.900

         TOTAL COEFFICIENT OF DETERMINATION FOR Y - VARIABLES IS  1.000


         SQUARED MULTIPLE CORRELATIONS FOR X - VARIABLES
            age         sex         rmarst      rf
          ________    ________    ________    ________
            1.000       1.000       1.000       0.900

         SQUARED MULTIPLE CORRELATIONS FOR STRUCTURAL EQUATIONS
            educ        tinc        swj         xraysc      mhaq
          ________    ________    ________    ________    ________
            0.225       0.560       0.125       0.175       0.280

         TOTAL COEFFICIENT OF DETERMINATION FOR STRUCTURAL EQUATIONS  IS  0.630



                   MEASURES OF GOODNESS OF FIT FOR THE WHOLE MODEL :
-     CHI-SQUARE WITH  15 DEGREES OF FREEDOM IS     13.39 (PROB. LEVEL = 0.572)
-                           GOODNESS OF FIT INDEX IS 0.977
-                      ADJUSTED GOODNESS OF FIT INDEX IS 0.966
-                        ROOT MEAN SQUARE RESIDUAL IS     0.340
```

```
-MODIFICATION INDICES

         BETA
            educ        tinc        swj         xraysc      mhaq
         --------    --------    --------    --------    --------
 educ       0.000       0.395       1.203       0.030       1.433
 tinc       0.000       0.000       0.028       0.502       0.995
 swj        0.953       1.608       0.000       0.873       1.120
 xraysc     0.028       0.385       0.000       0.000       0.021
 mhaq       0.000       0.000       0.000       0.106       0.000

         GAMMA
            age         sex         rmarst      rf
         --------    --------    --------    --------
 educ       0.000       0.000       0.395       0.002
 tinc       0.000       0.000       0.000       3.849
 swj        0.021       0.000       1.608       0.000
 xraysc     0.000       2.455       0.030       0.000
 mhaq       0.000       0.098       1.807       0.174

         PHI
            age         sex         rmarst      rf
         --------    --------    --------    --------
 age        0.000
 sex        0.000       0.000
 rmarst     0.000       0.000       0.000
 rf         0.000       0.000       0.000       0.000

         PSI
            educ        tinc        swj         xraysc      mhaq
         --------    --------    --------    --------    --------
            0.000       0.000       0.000       0.000       0.000

         THETA EPS
            educ        tinc        swj         xraysc      mhaq
         --------    --------    --------    --------    --------
            1.786       1.736       1.040       0.000       0.000

         THETA DELTA
            age         sex         rmarst      rf
         --------    --------    --------    --------
            2.013       0.028       3.849       0.772

         MAXIMUM MODIFICATION INDEX IS    3.85 FOR ELEMENT ( 3, 3) OF THETA DELTA



 STANDARD ERRORS

         BETA
            educ        tinc        swj         xraysc      mhaq
         --------    --------    --------    --------    --------
 educ       0.000       0.000       0.000       0.000       0.000
 tinc       0.058       0.000       0.000       0.000       0.000
 swj        0.000       0.000       0.000       0.000       0.000
 xraysc     0.000       0.000       0.143       0.000       0.000
 mhaq       0.017       0.024       0.007       0.000       0.000

         GAMMA
            age         sex         rmarst      rf
         --------    --------    --------    --------
 educ       0.017       0.495       0.000       0.000
 tinc       0.011       0.290       0.285       0.000
 swj        0.000       1.027       0.000       1.062
 xraysc     0.051       0.000       0.000       1.630
 mhaq       0.003       0.000       0.000       0.000
```

```
          PHI
              age         sex         rmarst      rf
            ----------  ----------  ----------  ----------
age             22.445
sex              0.546       0.026
rmarst           0.555       0.019       0.027
rf               0.589       0.020       0.021       0.031

          PSI
              educ        tinc        swj         xraysc      mhaq
            ----------  ----------  ----------  ----------  ----------
                 0.816       0.265       3.523       7.184       0.021

          THETA EPS
              educ        tinc        swj         xraysc      mhaq
            ----------  ----------  ----------  ----------  ----------
                 0.000       0.000       0.000       0.000       0.000

          THETA DELTA
              age         sex         rmarst      rf
            ----------  ----------  ----------  ----------
                 0.000       0.000       0.000       0.000



-T-VALUES

         BETA
              educ        tinc        swj         xraysc      mhaq
            ----------  ----------  ----------  ----------  ----------
educ             0.000       0.000       0.000       0.000       0.000
tinc             3.948       0.000       0.000       0.000       0.000
swj              0.000       0.000       0.000       0.000       0.000
xraysc           0.000       0.000       4.137       0.000       0.000
mhaq            -0.542      -2.641       4.077       0.000       0.000

          GAMMA
              age         sex         rmarst      rf
            ----------  ----------  ----------  ----------
educ            -5.531      -0.860       0.000       0.000
tinc            -3.490      -1.406      -7.544       0.000
swj              0.000      -1.455       0.000       3.618
xraysc           1.594       0.000       0.000      -0.104
mhaq             1.562       0.000       0.000       0.000

          PHI
              age         sex         rmarst      rf
            ----------  ----------  ----------  ----------
age              7.969
sex              0.864       7.969
rmarst           1.140      -2.389       7.969
rf              -1.294       0.852      -1.732       7.171

          PSI
              educ        tinc        swj         xraysc      mhaq
            ----------  ----------  ----------  ----------  ----------
                 6.969       6.220       6.983       6.892       6.711

          THETA EPS
              educ        tinc        swj         xraysc      mhaq
            ----------  ----------  ----------  ----------  ----------
                 0.000       0.000       0.000       0.000       0.000

          THETA DELTA
              age         sex         rmarst      rf
            ----------  ----------  ----------  ----------
                 0.000       0.000       0.000       0.000
```

```
-TOTAL EFFECTS

          TOTAL EFFECTS OF KSI ON  ETA
             age         sex         rmarst      rf
          ________    ________    ________    ________
 educ       -0.094      -0.425       0.000       0.000
 tinc       -0.060      -0.505      -2.153       0.000
 swj         0.000      -1.494       0.000       3.841
 xraysc      0.081      -0.884       0.000       2.104
 mhaq        0.010      -0.007       0.137       0.112

          TOTAL EFFECTS OF KSI ON  Y
             age         sex         rmarst      rf
          ________    ________    ________    ________
 educ       -0.094      -0.425       0.000       0.000
 tinc       -0.060      -0.505      -2.153       0.000
 swj         0.000      -1.494       0.000       3.841
 xraysc      0.081      -0.884       0.000       2.104
 mhaq        0.010      -0.007       0.137       0.112

          TOTAL EFFECTS OF ETA ON  ETA
             educ        tinc        swj         xraysc      mhaq
          ________    ________    ________    ________    ________
 educ        0.000       0.000       0.000       0.000       0.000
 tinc        0.229       0.000       0.000       0.000       0.000
 swj         0.000       0.000       0.000       0.000       0.000
 xraysc      0.000       0.000       0.592       0.000       0.000
 mhaq       -0.024      -0.064       0.029       0.000       0.000

-LARGEST EIGENVALUE OF (I-BETA)*(I-BETA)-TRANSPOSED (STABILITY INDEX) IS   0.351



-FIRST ORDER DERIVATIVES

          BETA
             educ        tinc        swj         xraysc      mhaq
          ________    ________    ________    ________    ________
 educ        0.000      -0.021       0.191       0.044       0.007
 tinc        0.000       0.000      -0.051       0.316       0.016
 swj         0.042       0.039       0.000      -0.022      -0.004
 xraysc     -0.004       0.012      -0.000      -0.000       0.001
 mhaq       -0.000      -0.000      -0.000       0.466      -0.000

          GAMMA
             age         sex         rmarst      rf
          ________    ________    ________    ________
 educ        0.000      -0.000       0.010      -0.001
 tinc       -0.000      -0.000      -0.000      -0.052
 swj         0.032       0.000      -0.010       0.000
 xraysc     -0.000      -0.008       0.001       0.000
 mhaq        0.000      -0.031       0.105       0.037

          PHI
             age         sex         rmarst      rf
          ________    ________    ________    ________
 age         0.000
 sex        -0.000       0.000
 rmarst      0.000      -0.000      -0.000
 rf          0.000      -0.000      -0.000      -0.000

          PSI
             educ        tinc        swj         xraysc      mhaq
          ________    ________    ________    ________    ________
 educ        0.000
 tinc        0.000      -0.000
 swj         0.008       0.006      -0.000
 xraysc     -0.001       0.007      -0.001      -0.000
 mhaq       -0.002       0.129      -0.008       0.010      -0.000
```

```
         THETA EPS
            educ       tinc       swj        xraysc     mhaq
          --------   --------   --------   --------   --------
 educ       -0.001
 tinc       -0.001      0.016
 swj         0.009     -0.003      0.001
 xraysc     -0.003      0.007     -0.001     -0.000
 mhaq       -0.032      0.129     -0.013      0.010     -0.000

         THETA DELTA
            age        sex        rmarst     rf
          --------   --------   --------   --------
 age        -0.000
 sex         0.006      0.006
 rmarst     -0.004     -0.014     -0.150
 rf         -0.016     -0.095     -0.396      0.046


-STANDARDIZED SOLUTION

         LAMBDA Y
            educ       tinc       swj        xraysc     mhaq
          --------   --------   --------   --------   --------
 educ        2.708      0.000      0.000      0.000      0.000
 tinc        0.000      1.935      0.000      0.000      0.000
 swj         0.000      0.000      5.302      0.000      0.000
 xraysc      0.000      0.000      0.000      7.748      0.000
 mhaq        0.000      0.000      0.000      0.000      0.439

         LAMBDA X
            age        sex        rmarst     rf
          --------   --------   --------   --------
 age        13.374      0.000      0.000      0.000
 sex         0.000      0.459      0.000      0.000
 rmarst      0.000      0.000      0.465      0.000
 rf          0.000      0.000      0.000      0.468

        BETA
            educ       tinc       swj        xraysc     mhaq
          --------   --------   --------   --------   --------
 educ        0.000      0.000      0.000      0.000      0.000
 tinc        0.320      0.000      0.000      0.000      0.000
 swj         0.000      0.000      0.000      0.000      0.000
 xraysc      0.000      0.000      0.405      0.000      0.000
 mhaq       -0.057     -0.281      0.353      0.000      0.000

         GAMMA
            age        sex        rmarst     rf
          --------   --------   --------   --------
 educ       -0.463     -0.072      0.000      0.000
 tinc       -0.269     -0.097     -0.518      0.000
 swj         0.000     -0.129      0.000      0.339
 xraysc      0.139      0.000      0.000     -0.010
 mhaq        0.156      0.000      0.000      0.000

         PHI
            age        sex        rmarst     rf
          --------   --------   --------   --------
 age         1.000
 sex         0.077      1.000
 rmarst      0.102     -0.217      1.000
 rf         -0.122      0.080     -0.164      1.000

         PSI
            educ       tinc       swj        xraysc     mhaq
          --------   --------   --------   --------   --------
             0.775      0.440      0.875      0.825      0.720
         CORRELATION MATRIX FOR ETA
            educ      tinc      swj       xraysc    mhaq
           --------  --------  --------  --------  --------
 educ        1.000
 tinc        0.473     1.000
 swj         0.031     0.048     1.000
 xraysc     -0.053    -0.049     0.394     1.000
 mhaq       -0.253    -0.366     0.329     0.175     1.000

         CORRELATION MATRIX FOR Y
            educ      tinc      swj       xraysc    mhaq
           --------  --------  --------  --------  --------
 educ        1.000
 tinc        0.473     1.000
 swj         0.031     0.048     1.000
 xraysc     -0.053    -0.049     0.394     1.000
 mhaq       -0.253    -0.366     0.329     0.175     1.000

         REGRESSION MATRIX ETA ON KSI (STANDARDIZED)
            age       sex       rmarst    rf
           --------  --------  --------  --------
 educ       -0.463    -0.072     0.000     0.000
 tinc       -0.417    -0.120    -0.518     0.000
 swj         0.000    -0.129     0.000     0.339
 xraysc      0.139    -0.052     0.000     0.127
 mhaq        0.300    -0.008     0.145     0.120

         REGRESSION MATRIX Y ON X (STANDARDIZED)
            age       sex       rmarst    rf
           --------  --------  --------  --------
 educ       -0.463    -0.072     0.000     0.000
 tinc       -0.417    -0.120    -0.518     0.000
 swj         0.000    -0.129     0.000     0.339
 xraysc      0.139    -0.052     0.000     0.127
 mhaq        0.300    -0.008     0.145     0.120


     32 COMMAND LINES READ.
      0 ERRORS DETECTED.
      0 WARNINGS ISSUED.
      3 SECONDS CPU TIME.
     11 SECONDS ELAPSED TIME.
        END OF JOB.
```